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Synthesis of new compounds containing the 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine heterocyclic system as a substructure

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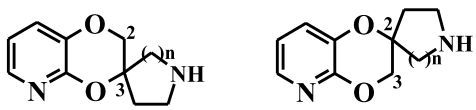
Abstract—2,3-Dihydro-spiro[1,4]dioxino[2,3-*b*]pyridine-3,3′-pyrrolidine (**8A**) and 2,3-dihydro-spiro[1,4]dioxino[2,3-*b*]pyridine-3,4′-piperidine (**9A**) have been synthesized from 2-chloro-3-pyridinol. The corresponding 2,3′ (**8B**) and 2,4′ (**9B**) isomers were obtained via the Smiles rearrangement, while **9B** was also selectively synthesized from 2-nitro-3-pyridinol. The separation of the isomers **A** and **B** under the sulfamide form was carried out by flash column chromatography. Subsequent transformations of the corresponding dioxinopyridine derivatives were described.

1. Introduction

Serotonin (5-HT) is an important neurotransmitter that mediates a wide variety of physiological responses in both peripheral and central nervous systems. The receptors activated by 5-HT have been divided into at least seven classes (5-HT$_1$–5-HT$_7$) and each class has been further divided into different subtypes.[1] Among them, the 5-HT$_{1A}$ receptor is one of the best studied; it is generally accepted that it is implicated in numerous physiological and pathological processes including the regulation of cognition, psychosis, anxiety, feeding satiety, temperature regulation, depression sleep, pain perception and sexual activity.[2]

Many structurally different compounds showed high affinity and selectivity for 5-HT$_{1A}$ receptors.[3] Nevertheless, it was noticed that the 2,3-dihydro-1,4-benzodioxin moiety is found in several compounds exhibiting high affinity for 5-HT$_{1A}$ receptors, such as MDL72832,[4] Spiroxatrine,[5] Flesinoxan,[6] HT-90[7] and MKC-242.[8]

In connection with the development of new potential 5-HT$_{1A}$ ligands, we have described the synthesis and the pharmacological activity of aza-analogues of MDL72832.[9,10] Now, in continuation of our research program concerning the dioxinopyridines,[11] we report here the preparation and the pharmacological activity of spiro dioxino–pyridine–pyrrolidine and spiro dioxino–pyridine–piperidine derivatives functionalized at the oxygenated moiety in position 3 (**A**) or position 2 (**B**) (Fig. 1). These new ring systems could be regarded as analogues of spiro(benzofurane)[12] and spiro(benzoindole) ones.[13]



8A (n = 1) **8B** (n = 1)
9A (n = 2) **9B** (n = 2)

Figure 1.

2. Results and discussion

Our initial attempts at the synthesis of spiro dioxino–pyridine–pyrrolidines **6** and spiro dioxino–pyridine–piperidines **7** were directed to the formation of the dioxino–pyridine system.

Accordingly, the 2-chloro-3-hydroxypyridine **1** was treated with NaH/DMF, forming in situ the corresponding alkoxide, which reacted with the appropriate epoxide **2** or **3** obtained by the known procedure[14] to afford the corresponding tertiary alcohol **4** or **5**. Then, **4** or **5** was cyclised to the spiro compound **6** or **7** using a basic treatment, which induced a

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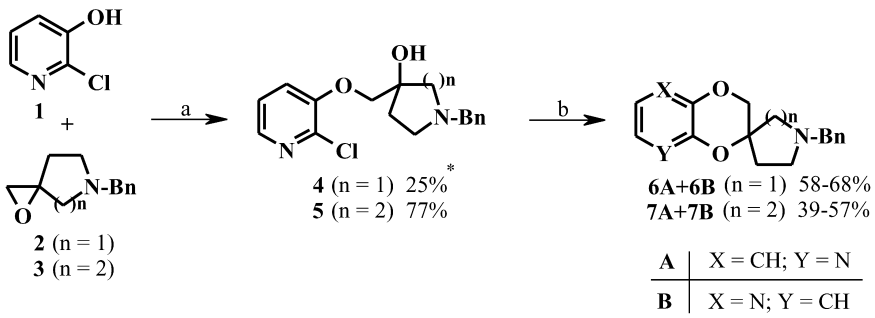


Scheme 1. *Reaction conditions*: (a) NaH, DMF, 120°C; (b) base, solvent, *T* (°C), *t* (h) (see Table 1). *The desired alcohol **4** was obtained in 25% yield along with a small amount of cyclic isomers **6** (10%) and the starting material **2** which was recovered in 25% yield.

Table 1. Conditions for the cyclization of the compounds **4** and **5**

Base/solvent	*T*/*t* (°C)/h	Compound **6**[a]		Compound **7**[b]	
		Yield[c] (%)	Ratio[d] (**A**/**B**)	Yield[c] (%)	Ratio[d] (**A**/**B**)
NaH/DME	80/*t*[e]	60	90/10	51	45/55
NaH/THF	55/*t*[f]	62	95/5	53	65/35
NaH/THF–HMPT	55/24	58	20/80	57	0/100
NaH/DMF	80/24	60	5/95	44	0/100
t-BuOK/*t*-BuOH	80/24	63	20/80	39	0/100

[a] From the alcohol **4**.
[b] From the alcohol **5**.
[c] Yields of mixture **6A+6B** (or **7A+7B**) isolated after filtration on silica gel column chromatography.
[d] Ratio of each isomer determined from ^{1}H NMR comparison of absorption areas of the CH_2-dioxinopyridine ring.
[e] 24 h for **4** and 8 h for **5**.
[f] 24 h for **4** and 10 h for **5**.

nucleophilic displacement of chlorine atom (Scheme 1). Different experimental conditions selected for the cyclization of compounds **4** were studied. They always led to a mixture of **A** and **B** isomers, proved to be non-separable by silica gel column chromatography (Table 1).

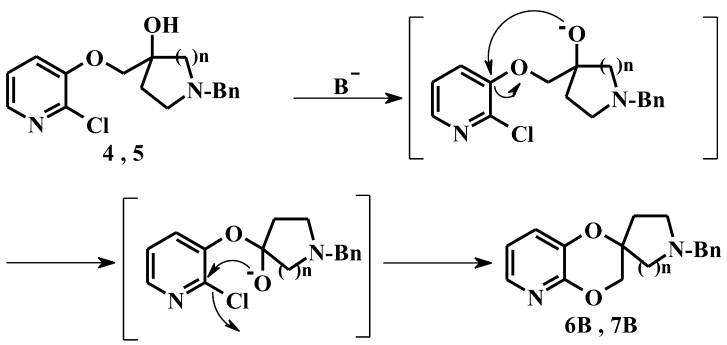
Similarly, a mixture of **7A** and **7B** isomers was obtained when **5** was treated with NaH/DME or NaH/THF. Conversely, only the isomer **7B** was isolated under other conditions (NaH/THF–HMPT, NaH/DMF, *t*-BuOK/*t*-BuOH). The best yields were obtained with a THF–HMPT mixture as solvent. The experimental data used in the conversion of **5** into the spiro dioxino–pyridine piperidines **7** are shown in Table 1.

The formation of the **B** isomer (Scheme 2) can be explained by an intramolecular nucleophilic substitution at the 3 position of the pyridine ring with displacement of the alkoxide, and the subsequent closure of the delivered alkoxide into the 2 position of the pyridine ring.[15] This reaction known as the Smiles rearrangement[16] is usually carried out on deactivated compounds such as pyridinyl or nitrophenyl derivatives.

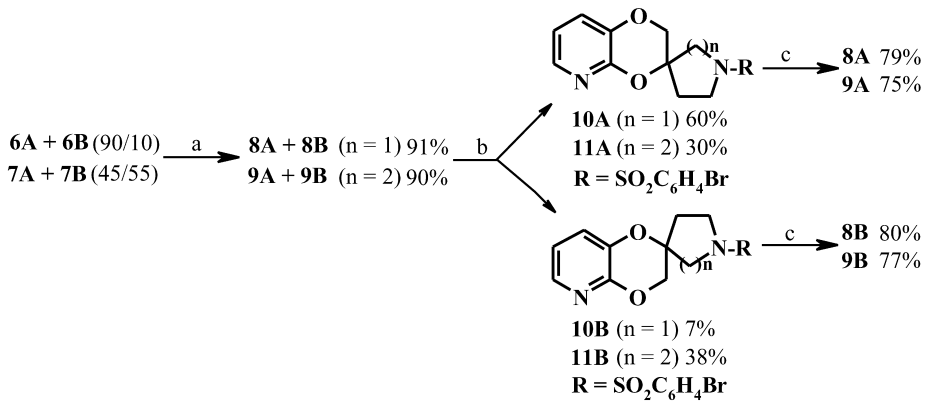
The ^{1}H NMR spectrum of a (**7A+7B**) isomers mixture presents two singlets at 3.89 and 4.09 ppm (O–CH_2–C). Ratio of each isomer was determined from ^{1}H NMR comparison of integration intensity of these two singlets (Table 1).

The availability of both isomers **6** and **7** was ensured by the formation of their sulfamide derivatives **10** and **11** suitable for column chromatography separation on silica gel. Thus, each mixture of (**6A+6B**) or (**7A+7B**), resulting from the cyclization by NaH/DME, was transformed into the corresponding amines **8** or **9** by catalytic 10% Pd/C hydrogenolysis in MeOH with a few drops of concentrated hydrochloric acid, in 91 and 90% yield, respectively. It's worth to note that both isomeric mixtures (**8A+8B**) and (**9A+9B**) cannot be separated by column chromatography. Thereafter, treatment of both isomeric mixtures with *p*-bromobenzenesulfonyl chloride in the presence of Et_3N in DMF at 60°C gave the corresponding sulfamides **10** or **11** in a 70% total yield (Scheme 3). Finally, the **10A** and **10B** isomers (or **11A** and **11B**) were easily separated by column chromatography.

In order to assign the structures, we performed 2D NMR



Scheme 2.



Scheme 3. *Reaction conditions*: (a) H_2, 10% Pd/C, HCl, MeOH; (b) (i) *p*-$BrC_6H_4SO_2Cl$, Et_3N, DMF, 60°C, (ii) flash chromatography; (c) $LiAlH_4$, DME, reflux.

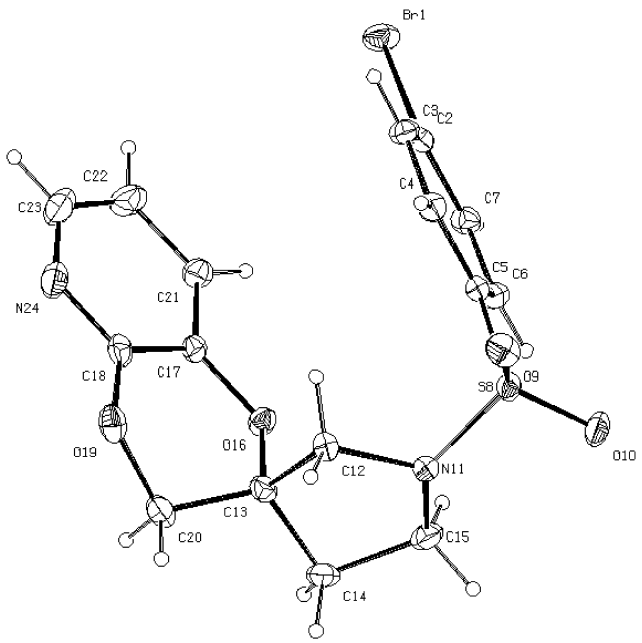


Figure 2. The ORTEP drawing of **10B** with thermal ellipsoids at 30% level.

experiments (HMQC and HMBC) for compounds **10A**, **10B**, **11A** and **11B**. Moreover, the structure of **10B** and **11B** was established by X-ray diffraction, clearly identifying the substitution position on the dioxine ring (Figs. 2 and 3). Both compounds are racemic mixtures as indicated by the spatial groups. In the solid state, the conformation of **10B** is folded, with an angle between the pyridine plan and the phenyl one=39.3(2)°. Moreover, a chelate is formed with a bond between C(4)H(4) and O(9): C(4)H(4)–O(9)=2.88(5)Å and H(4)–O(9)=2.51 Å, the angle C(4) H(4) O(9) is 104.6°. Consequently, the orientation of the phenyl ring is blocked with respect to the sulfur atom.

The same phenomenum is found for **11B**. A chelate is defined by two intramolecular bonds: C(12)H(12)–O(9)=2.922(7) Å and H(12)–O(9)=2.48 Å; C(16)H(16)–O(10)=2.881(7) Å and H(16)–O(10)=2.42 Å, leading to a blocked conformation of the molecule. There are four independent molecules in the cell unit, all in a folded form with angles between the phenyl ring and the pyridine varying from 65.9(2)°, 66.9(2)°, 67.7(2)° to 74.6(2)°.

Such results enlightening the folded molecular could be discussed in terms of preliminary structure–activity

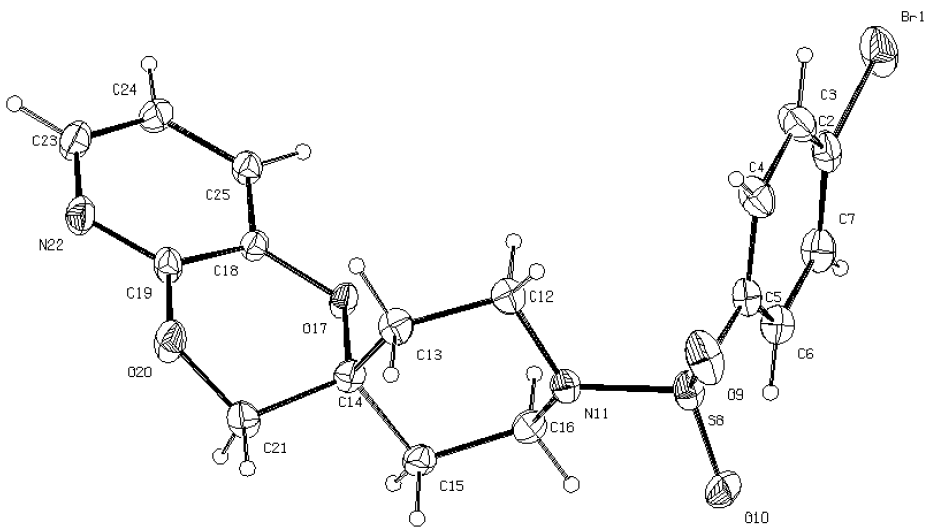
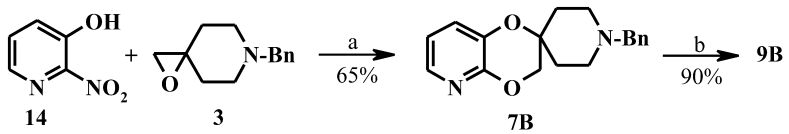


Figure 3. The ORTEP drawing of **11B** with thermal ellipsoids at 30% level.



Scheme 4. *Reaction conditions*: (a) NaH, DMF, 120°C, 36 h; (b) H_2, 10% Pd/C, HCl, MeOH.

relationships. Hence, as previously described for hypothetical HT_{1A} receptor,[17] the pocket available for binding seems to give restricted spatial access to the ligand since only pseudo-linear compounds are well-tolerated. Moreover, this hypothesis is confirmed by recently published results exploring the computational three dimensional structure of the receptor, constructed from the crystal structure of bovine rhodopsin.[18,19] Consequently, the folded conformation of **10B** and **11B** could be found detrimental for a 5-HT_{1A} activity.

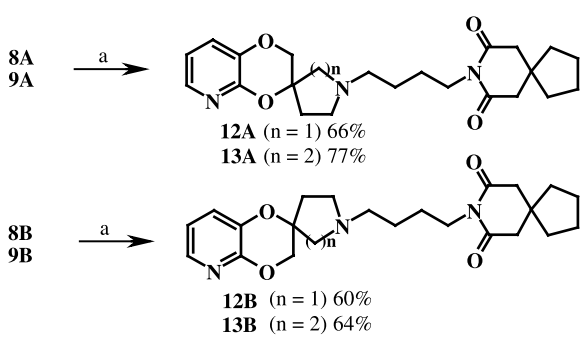
The removal of the sulfamide function of each isomer **10A**, **10B** and **11A**, **11B** was achieved under soft conditions described by Tuladhar et coll.,[20] using $LiAlH_4$ in DME under reflux overnight. This sequence afforded the amines **8A**, **8B** and **9A**, **9B** in 79, 80, 75 and 77% yields, respectively (Scheme 3).

As depicted in Scheme 4, a new way towards the synthesis of compound **9B** was explored, starting from 2-nitro-3-pyridinol (**14**). Compound **7B** was prepared in 65% yield, via a Smiles rearrangement, by condensation of the anion of **14** on the epoxide **3**, using NaH in DMF at 120°C. Then, **9B** was obtained in a good yield (90%) through catalytic Pd/C hydrogenolysis of **7B**.

On the other hand, the various attempts for the condensation of 2-nitro-3-pyridinol (**14**) on the epoxide **2** achieved under several conditions failed. In all cases, the starting material **2** was recovered or degradation products were detected.

Finally, we prepared **12A**, **12B**, **13A** and **13B** in acceptable yields by alkylation of the corresponding **8A**, **8B**, **9A** and **9B** with 8-(4-bromobutyl)-8-azaspiro[4,5]decane-7,9-dione[21] in DMF, in the presence of Et_3N at 60°C (Scheme 5).

Compounds **10A**, **11A**, **12A** and **13A** and their corresponding **B** isomers were tested as potential SNC agents. However, none of them showed any noticeable affinity for the 5-HT_{1A} serotonin receptors.



Scheme 5. *Reaction conditions*: (a) 8-(4-Bromobutyl)-8-azaspiro[4,5]-decane-7,9-dione, DMF, Et_3N, KI, 60°C.

3. Conclusion

This study reports a convenient and effective synthetic route to isomeric 2- and 3-substituted-2,3-dihydro-spiro[1,4]dioxino[2,3-*b*]pyridine amino derivatives **12A**, **12B** and **13A**, **13B**, developed as potential 5-HT_{1A} ligands. The ratio of both **A** and **B** isomers of spiro compound **6** or **7** was shown to be greatly affected by the experimental conditions chosen for the cyclization of the intermediates **4** and **5**. It was observed that the conversion of the **A** and **B** isomers of amine **8** or **9** into the corresponding sulfamides (**10** or **11**) constitutes an interesting way for the subsequent chromatographic separation of each isomer.

The structures of **10B** and **11B** were established by X-ray crystallography. Data were discussed in terms of a preliminary understanding of structure–activity relationships concerning their affinity for the 5-HT_{1A} serotonin receptor.

4. Experimental

^1H and ^{13}C NMR spectra were, respectively, recorded at 250 and 62.9 MHz on a Bruker Avance DPX250. Chemical shifts (δ values) were reported in ppm and coupling constants (J values) in Hz. Me_4Si was the internal standard. IR spectra were obtained with a Perkin–Elmer FT Paragon 1000PC. Elemental analyses were performed by CNRS laboratory (Vernaison, France) and Serveis Científico-Tècnics de la Universitat de Barcelona (Spain). MS data were taken on a Perkin–Elmer SCIEX type API 300. Melting points were determined in capillary tubes with Büchi SMP-20 or on a Köfler apparatus and are uncorrected. TLC and flash chromatography separations were respectively performed on silica gel (Merck 60 F_{254}) plates and on silica gel (Merck 60, 230–400 mesh) columns. All reactions involving moisture-sensitive reagents were performed under an argon atmosphere. 8-(4-Bromobutyl)-8-azaspiro[4,5]decane-7,9-dione was prepared by condensation of the anion of tetramethyleneglutarimide with 1,4-dibromobutane using K_2CO_3 in CH_3CN at 60°C for 24 h according to the method described in the literature.[21] All organic solvents were distilled immediately prior to use, and magnesium sulfate was used for drying solutions of organic solvents.

The solid state of **10B** and **11B** compounds have been determined by single-crystal X-ray diffraction techniques. The data were collected on a CAD4 Enraf-Nonius diffractometer with graphite monochromatized Cu Ka radiation. The cell parameters were determined by least-squares from the setting angles for 25 reflexions.

The positions of non-H atoms were determined by the program SHELXS 86[22] and the position of the H atoms were deduced from coordinates of the non-H atoms and

confirmed by Fourier synthesis. H atoms were included for structure factor calculations but not refined. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Centre (CCDC), UK as Supplementary Materials.[23]

4.1. General procedure for the preparation of the alcohols 4 and 5

To a suspension of NaH (335 mg of 60% oil dispersion, 14.78 mmol) in DMF (10 mL) was added dropwise a solution of 2-chloro-3-hydroxypyridine (1.24 g, 9.6 mmol) in DMF (10 mL). After 15 min, a solution of epoxide **2** or **3** (9.5 mmol) in DMF (10 mL) was added and the mixture was stirred at 120°C during 30 min and 36 h for **2** and **3**, respectively. After cooling to room temperature, the DMF was evaporated to dryness. The residue was washed with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated and chromatographed (eluent: MeOH/CH_2Cl_2, 1:9) to give the alcohol **4** (25%) or **5** (77%).

4.1.1. 2-Chloro-3-(*N*-benzyl-3′-pyrrolidinol-3′-methoxy)-pyridine 4. Oil; IR (film) ν 3500–3180 (OH), 1286 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85–2.00 (m, 1H, CH_2–CH_2–N), 2.02–2.15 (m, 1H, CH_2–CH_2–N), 2.50–2.62 (m, 1H, C–CH_2–N), 2.64–2.88 (m, 3H, CH_2–CH_2–N, C–CH_2–N), 3.60 (s, 2H, N–CH_2–Ph), 3.97 (s, 2H, O–CH_2–C), 4.01 (s, 1H, OH), 7.07–7.40 (m, 7H, H_β, H_γ, H_{arom}), 7.93 (dd, 1H, J=1.7, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 36.9 (CH_2), 53.2 (CH_2), 60.4 (CH_2), 64.3 (CH_2), 75.1 (CH_2), 79.3 (C), 121.3 (CH), 123.6 (CH), 127.5 (CH), 128.7 (2CH), 129.3 (2CH), 138.7 (CH), 141.5 (CH), 141.6 (C), 151.3 (C); MS (CI) m/z 319 (M+1); Anal. calcd for $C_{17}H_{19}N_2O_2Cl$: C 64.05, H 6.01, N 8.79, found: C 64.01, H 5.97, N 8.75.

4.1.2. 2-Chloro-3-(*N*-benzyl-4′-piperidinol-4′-methoxy)-pyridine 5. Oil; IR (film) ν 3500–3200 (OH), 1285 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75–1.95 (m, 4H, 2×CH_2–CH_2–N), 2.43–2.63 (m, 3H, CH_2–CH_2–N, OH), 2.68–2.85 (m, 2H, C–CH_2–N), 3.63 (s, 2H, N–CH_2–Ph), 3.94 (s, 2H, O–CH_2–C), 7.20–7.75 (m, 7H, H_β, H_γ, H_{arom}), 8.06 (dd, 1H, J=2.6, 3.6 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 33.8 ($2CH_2$), 48.7 ($2CH_2$), 63.0 (CH_2), 68.9 (CH_2), 76.9 (C), 120.6 (CH), 123.1 (CH), 126.9 (CH), 128.1 (2CH), 129.1 (2CH), 138.3 (C), 140.9 (CH), 141.1 (C), 150.8 (C); MS (CI) m/z 333 (M+1); Anal. calcd for $C_{18}H_{21}N_2O_2Cl$: C 64.95, H 6.36, N 8.42, found: C 64.87, H 6.41, N 8.51.

4.2. General procedure for the preparation of dioxinopyridines 6 and 7

To a solution of appropriate base (NaH or *t*-BuOK, 3 mmol) in solvent (DME, THF, THF–HMPT 85:15, DMF or *t*-BuOH, 5 mL) was added **3** or **4** (1.5 mmol). The resulting mixture was heated (55–80°C) for 8–14 h. After cooling to room temperature, The reaction was hydrolysed with H_2O and extraced with AcOEt. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue which was purified by flash chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford an inseparable mixture of two isomers **6A** and **6B** (58–68%) or **7A** and **7B** (39–57%) (see Table 1).

4.2.1. 2,3-Dihydro-1′-benzylspiro(1,4-dioxino[2,3-*b*]pyridine)-3,3′-pyrrolidine and 2,3-dihydro-1′-benzylspiro(1,4-dioxino[2,3-*b*]pyridine)-2,3′-pyrrolidine 6A+6B. Oil; IR (film) ν 1270 and 1185 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92–2.18 (m, 2H, CH_2–CH_2–N), 2.60–2.99 (m, 4H, C–CH_2–N, CH_2–CH_2–N), 3.63 (d, 1H, J=13.0 Hz, N–CH_2–Ph), 3.78 (d, 1H, J=13.0 Hz, N–CH_2–Ph), 3.92 (d, 1H, J=11.3 Hz, O–CH_2–C for **6A**), 4.06 (d, 1H, J=11.3 Hz, O–CH_2–C for **6B**), 4.16 (d, 1H, J=11.3 Hz, O–CH_2–C for **6A**), 4.30 (d, 1H, J=11.3 Hz, O–CH_2–C for **6B**), 6.84 (dd, 1H, J=4.9, 7.8 Hz, H_β), 7.17 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.20–7.40 (m, 5H, H_{arom}), 7.82 (dd, 1H, J=1.6, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 29.9 (CH_2), 49.1 (CH_2), 59.4 (CH_2), 61.8 (CH_2), 63.5 (CH_2), 74.1 (C), 116.6 (CH), 121.5 (CH), 127.1 (CH), 128.5 (CH), 129.6 (CH),138.7 (C), 140.8 (C), 146.3 (CH), 157.3 (C); MS (CI) m/z 283 (M+1).

4.2.2. 2,3-Dihydro-1′-benzylspiro(1,4-dioxino[2,3-*b*]pyridine)-3,4′-piperidine and 2,3-dihydro-1′-benzylspiro(1,4-dioxino[2,3-*b*]pyridine)-2,4′-piperidine 7A+7B. Oil; IR (film) ν 1270 and 1190 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–1.92 (m, 4H, CH_2–CH_2–N), 2.51–2.71 (m, 4H, CH_2–CH_2–N), 3.55 (s, 2H, N–CH_2–Ph), 3.89 (s, 2H, O–CH_2–C for **7A**), 4.09 (s, 2H, O–CH_2–C for **7B**), 6.82 (dd, 1H, J=4.9, 7.8 Hz, H_β), 7.15 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.21–7.33 (m, 5H, H_{arom}), 7.82 (dd, 1H, J=1.6, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 31.8 (CH_2), 48.3 (CH_2), 63.1 (CH_2), 71.1 (CH_2), 73.4 (C), 118.1 (CH), 124.5 (CH), 127.4 (CH), 127.5 (CH), 129.3 (CH), 138.4 (C), 138.5 (C), 140.5 (CH), 150.3 (C); MS (CI) m/z 297 (M+1).

4.3. General procedure for the preparation of the sulfamides 10 and 11

A solution of dioxinopyridines **6** or **7** (0.68 mmol) in MeOH (25 mL) with a few drops of HCl was shaken with Pd/C (10%, 20 mg) under hydrogen atmosphere. When the reaction was complete, the catalyst was removed by filtration and the combined filtrate was concentrated in vacuo to give **8** or **9** in 91% yield. Spectral data will be given further for each isolated isomer **A** and **B** after their separation.

To a solution of amines **8** or **9** (10 mmol) in DMF (15 mL) were added *p*-bromobenzenesulfonyl chloride (3829 mg, 15 mmol) in DMF (5 mL) and Et_3N (4.2 mL, 30 mmol). The mixture was heated at 60°C until total consumption of amine. The solvent was removed under reduced pressure and the separation of the mixture of the two isomers **10A** and **10B** (or **11A** and **11B**) was carried out by flash column chromatography (eluent: AcOEt/petroleum, 3:7). The yields of each isomer **10A**, **10B**, **11A** and **11B** were 60, 7, 30 and 38%, respectively.

4.3.1. 2,3-Dihydro-1′-*p*-bromobenzenesulfonylspiro(1,4-dioxino[2,3-*b*]pyridine)-3,3′-pyrrolidine 10A. Mp 224–225°C; IR (KBr) ν 1432 (SO_2), 1280 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06–2.13 (m, 2H, CH_2–CH_2–N), 3.25 (d, 1H, J=11.2 Hz, C–CH_2–N), 3.40 (td, 1H, J=7.4, 19.1 Hz, CH_2–CH_2–N), 3.57–3.70 (m, 2H, CH_2–CH_2–N, C–CH_2–N), 3.93 (d, 1H, J=11.3 Hz, O–CH_2–C), 4.15 (d, 1H, J=11.3 Hz, O–CH_2–C), 6.90 (dd, 1H, J=4.7, 7.8 Hz,

H_β), 7.21 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.60–7.75 (m, 4H, H_{arom}), 7.83 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 33.5 (CH_2), 4.68 (CH_2), 55.1 (CH_2), 68.7 (CH_2), 80.9 (C), 119.1 (CH), 125.7 (CH), 128.2 (C), 129.3 (CH), 132.6 (CH), 135.3 (C), 136.8 (C), 140.7 (CH), 150.0 (C); MS (CI) m/z 411 (M+1 for ^{79}Br), 413 (M+1 for ^{81}Br); Anal. calcd for $C_{16}H_{15}BrN_2O_4S$: C 46.72, H 3.67, N 6.81, found: C 46.88, H 3.62, N 6.98.

4.3.2. 2,3-Dihydro-1′-*p*-bromobenzenesulfonylspiro(1,4-dioxino[2,3-*b*]pyridine)-2,3′-pyrrolidine 10B. Mp 215–216°C; IR (KBr) ν 1435 (SO_2), 1285 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.99–2.20 (m, 2H, CH_2–CH_2–N), 3.26 (d, 1H, J=11.0 Hz, C–CH_2–N), 3.40 (td, 1H, J=7.5, 18.8 Hz, CH_2–CH_2–N), 3.56–3.72 (m, 2H, CH_2–CH_2–N, C–CH_2–N), 4.07 (d, 1H, J=11.2 Hz, O–CH_2–C), 4.29 (d, 1H, J=11.2 Hz, O–CH_2–C), 6.79 (dd, 1H, J=4.7, 7.8 Hz, H_β), 6.88 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.60–7.75 (m, 4H, H_{arom}), 7.84 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 34.0 (CH_2), 46.7 (CH_2), 55.3 (CH_2), 68.2 (CH_2), 82.0 (C), 119.1 (CH), 125.1 (CH), 128.5 (C), 129.1 (CH), 132.7 (CH), 135.0 (C), 138.1 (C), 140.9 (CH), 149.3 (C); MS (CI) m/z 411 (M+1 for ^{79}Br), 413 (M+1 for ^{81}Br); Anal. calcd for $C_{16}H_{15}BrN_2O_4S$: C 46.72, H 3.67, N 6.81, found: C 46.50, H 3.59, N 6.74.

4.3.3. 2,3-Dihydro-1′-*p*-bromobenzenesulfonylspiro(1,4-dioxino[2,3-*b*]pyridine)-3,4′-piperidine 11A. Mp 210–211°C; IR (KBr) ν 1430 (SO_2), 1290 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.74–2.00 (m, 4H, CH_2–CH_2–N), 2.86 (td, 2H, J=2.9, 12.0 Hz, CH_2–CH_2–N), 3.66–3.80 (m, 2H, CH_2–CH_2–N), 3.90 (s, 2H, O–CH_2–C), 6.86 (dd, 1H, J=4.9, 7.8 Hz, H_β), 7.19 (dd, 1H, J=1.7, 7.8 Hz, H_γ), 7.62 (dd, 2H, J=2.2, 6.6 Hz, H_{arom}), 7.68 (dd, 2H, J=2.2, 6.6 Hz, H_{arom}), 7.80 (dd, 1H, J=1.7, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 29.1 (CH_2), 42.1 (CH_2), 68.3 (CH_2), 82.0 (C), 117.6 (CH), 124.1 (CH), 127.5 (C), 129.0 (CH), 132.4 (CH), 135.7 (C), 137.0 (C), 140.0 (CH), 150.6 (C); MS (CI) m/z 425 (M+1 for ^{79}Br), 427 (M+1 for ^{81}Br); Anal. calcd for $C_{17}H_{17}BrN_2O_4S$: C 47.98, H 4.08, N 6.59, found: C 47.81, H 4.02, N 6.41.

4.3.4. 2,3-Dihydro-1′-*p*-bromobenzenesulfonylspiro(1,4-dioxino[2,3-*b*]pyridine)-2,4′-piperidine 11B. Mp 203–204°C; IR (KBr) ν 1427 (SO_2), 1291 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67–1.95 (m, 4H, CH_2–CH_2–N), 2.76 (td, 2H, J=3.4, 11.7 Hz, CH_2–CH_2–N), 3.58–3.72 (m, 2H, CH_2–CH_2–N), 4.06 (s, 2H, O–CH_2–C), 6.84 (dd, 1H, J=4.9, 7.9 Hz, H_β), 7.09 (dd, 1H, J=1.5, 7.9 Hz, H_γ), 7.64 (dd, 2H, J=2.1, 6.6 Hz, H_{arom}), 7.71 (dd, 2H, J=2.1, 6.6 Hz, H_{arom}), 7.81 (dd, 1H, J=1.5, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 30.7 (CH_2), 41.2 (CH_2), 70.5 (CH_2), 71.3 (C), 118.8 (CH), 125.1 (CH), 127.9 (C), 129.0 (CH), 132.4 (CH), 135.5 (C), 136.8 (C), 140.0 (CH), 159.9 (C); MS (CI) m/z 425 (M+1 for ^{79}Br), 427 (M+1 for ^{81}Br); Anal. calcd for $C_{17}H_{17}BrN_2O_4S$: C 47.98, H 4.08, N 6.59, found: C 47.90, H 3.98, N 6.54.

4.4. General procedure for the preparation of the amines 8 and 9

To stirred solution of sulfamides **10A**, **10B**, **11A** or **11B** (1.21 mmol) in DME (10 mL) was added dropwise $LiAlH_4$ (1140 mg, 3.63 mmol) in DME (5 mL). The mixture was heated to reflux during overnight. After cooling to room temperature, the reaction mixture was diluted in H_2O and extracted with AcOEt. The organic layer was dried and concentrated to give a residue, which was purified by flash column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford amines **8A**, **8B**, **9A** and **9B** in 79, 80, 75 and 77% yield, respectively.

4.4.1. 2,3-Dihydrospiro(1,4-dioxino[2,3-*b*]pyridine)-3,3′-pyrrolidine 8A. Oil; IR (film) ν 3600–3200 (NH), 1288 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98–2.06 (m, 2H, CH_2–CH_2–NH), 2.78 (d, 2H, J=11.2 Hz, C–CH_2–NH), 3.25–3.40 (m, 2H, CH_2–CH_2–NH), 4.12 (d, 1H, J=11.2 Hz, O–CH_2–C), 4.33 (d, 1H, J=11.2 Hz, O–CH_2–C), 6.88 (dd, 1H, J=4.9, 7.8 Hz, H_β), 7.23 (dd, 1H, J=1.7, 7.8 Hz, H_γ), 7.84 (dd, 1H, J=1.7, 4.9 Hz, H_α), 9.07 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.3 (CH_2), 45.8 (CH_2), 57.1 (CH_2), 63.9 (CH), 75.4 (C), 116.0 (CH), 121.6 (CH), 139.2 (C), 140.8 (CH), 149.9 (C); MS (CI) m/z 193 (M+1); Anal. calcd for $C_{10}H_{12}N_2O_2$: C 62.55, H 6.30, N 14.91, found: C 62.86, H 6.39, N 15.23.

4.4.2. 2,3-Dihydrospiro(1,4-dioxino[2,3-*b*]pyridine)-2,3′-pyrrolidine 8B. Oil; IR (film) ν 3600–3200 (NH), 1290 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (t, 2H, J=6.9 Hz, CH_2–CH_2–NH), 2.57–2.66 (m, 1H, CH_2–CH_2–NH), 2.71 (s, 2H, C–CH_2–NH), 2.80–2.91 (m, 1H, CH_2–CH_2–NH), 4.14 (d, 1H, J=11.5 Hz, O–CH_2–C), 4.36 (d, 1H, J=11.5 Hz, O–CH_2–C), 6.87 (dd, 1H, J=4.9, 7.8 Hz, H_β), 7.20 (dd, 1H, J=1.7, 7.8 Hz, H_γ), 7.82 (dd, 1H, J=1.7, 4.9 Hz, H_α), 9.03 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_2), 45.8 (CH_2), 57.1 (CH_2), 63.9 (CH), 75.3 (C), 116.0 (CH), 121.7 (CH), 139.1 (C), 140.8 (CH), 150.0 (C); MS (CI) m/z 193 (M+1); Anal. calcd for $C_{10}H_{12}N_2O_2$: C 62.55, H 6.30, N 14.91, found: C 62.71, H 6.41, N 15.17.

4.4.3. 2,3-Dihydrospiro(1,4-dioxino[2,3-*b*]pyridine)-3,4′-piperidine 9A. Oil; IR (film) ν 3600–3200 (NH), 1277 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80–2.10 (m, 4H, CH_2–CH_2–NH), 2.78–3.29 (m, 4H, CH_2–CH_2–NH), 4.07 (s, 2H, O–CH_2–C), 6.68 (dd, 1H, J=4.5, 7.8 Hz, H_β), 6.96 (dd, 1H, J=1.5, 7.8 Hz, H_γ), 7.74 (dd, 1H, J=1.5, 4.5 Hz, H_α), 9.10 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.1 (CH_2), 39.9 (CH_2), 69.5 (C), 70.9 (CH), 118.0 (CH), 124.6 (CH), 135.9 (C), 139.0 (CH), 150.0 (C); MS (CI) m/z 207 (M+1); Anal. calcd for $C_{11}H_{14}N_2O_2$: C 64.13, H 6.85, N 13.60, found: C 64.28, H 7.02, N 13.68.

4.4.4. 2,3-Dihydrospiro(1,4-dioxino[2,3-*b*]pyridine)-2,4′-piperidine 9B. Oil; IR (film) ν 3600–3200 (NH), 1287 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76–2.05 (m, 4H, CH_2–CH_2–NH), 2.92–3.30 (m, 4H, CH_2–CH_2–NH), 4.24 (s, 2H, O–CH_2–C), 6.98 (dd, 1H, J=4.7, 7.8 Hz, H_β), 7.36 (dd, 1H, J=1.5, 7.8 Hz, H_γ), 7.76 (dd, 1H, J=1.5, 4.7 Hz, H_α), 9.03 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 27.1 (CH_2), 38.3 (CH_2), 69.5 (C), 69.9 (CH), 118.7 (CH), 125.0 (CH), 136.5 (C), 139.1 (CH), 149.5 (C); MS (CI) m/z 207 (M+1); Anal. calcd for $C_{11}H_{14}N_2O_2$: C 64.13, H 6.85, N 13.60, found: C 64.35, H 6.80, N 13.34.

4.5. Preparation of the amine 9B from 2-nitro-3-hydroxypyridine 14

To a suspension of NaH (335 mg of 60% oil dispersion,

14.78 mmol) in DMF (10 mL) was added dropwise a solution 2-nitro-3-hydroxypyridine (**14**) (1.34 g, 9.6 mmol) in DMF (10 mL). After 15 min, a solution of epoxide **3** (1.5 g, 9.5 mmol) in DMF (10 mL) was added and the mixture was stirred at 120°C during 36 h. After cooling to room temperature, the DMF was evaporated to dryness. The residue was washed with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$, evaporated and purified by column chromatography (eluent: $MeOH/CH_2Cl_2$, 1:9) to give the **7B** (65%) as oil. Then, catalytic Pd/C hydrogenolysis of compound **7B** according to the procedure described for the preparation of **8** or **9** gave debenzylated product **9B** in good yield (90%). The analytical data were identical with those reported above.

4.6. General procedure for the preparation of the *N*-substituted amines 12 and 13

To a solution of each isolated isomer **8A**, **8B**, **9A** or **9B** (1.2 mmol) and 8-(4-bromobutyl)-8-azaspiro[4,5]decane-7,9-dione (43 mg, 1.4 mmol) in DMF (12 mL) were added Et_3N (0.5 mL, 6 mmol) and KI (40 mg, 0.20 mmol). The reaction was stirred at 60°C for 24 h and the solvent was then removed under reduced pressure. Water was added and then the suspension was extracted with AcOEt to give crude *N*-alkylamine. This was purified by flash column chromatography (eluent: CH_2Cl_2) to afford compounds **12A** (66%), **12B** (60%), **13A** (77%) and **13B** (64%).

4.6.1. 2,3-Dihydro-1′-[4-(8-azaspiro[4,5]decane-7,9-dione)butyl]spiro(1,4-dioxino[2,3-*b*]pyridine)-3,3′-pyrrolidine 12A. Oil; IR (film) ν 1715 and 1650 (NCO), 1280 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.77 (m, 12H, H_1, H_2, H_3, H_4, N–CH_2–(CH_2)$_2$–CH_2–N), 2.00–2.20 (m, 2H, CH_2–CH_2–N), 2.58 (s, 4H, H_6, H_{10}), 2.65–2.75 (m, 2H, CH_2–CH_2–N), 3.25–3.71 (m, 6H, C–CH_2–N, N–CH_2–(CH_2)$_3$–N, CH_2–N–CO), 3.95 (d, 1H, J=11.0 Hz, O–CH_2–C), 4.14 (d, 1H, J=11.0 Hz, O–CH_2–C), 6.86 (dd, 1H, J=4.8, 7.8 Hz, H_β), 7.25 (dd, 1H, J=1.5, 7.8 Hz, H_γ), 7.87 (dd, 1H, J=1.5, 4.8 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 24.1 (CH_2), 24.6 (CH_2), 25.8 (CH_2), 27.8 (CH_2), 31.2 (CH_2), 37.4 (CH_2), 39.3 (C), 39.6 (CH_2), 44.8 (CH_2), 48.4 (CH_2), 58.1 (CH_2), 71.3 (CH_2), 72.2 (C), 118.5 (CH), 124.9 (CH), 138.4 (CH), 139.8 (C), 150.1 (C), 172.2 (CO); MS (CI) *m*/*z* 414 (M+1); Anal. calcd for $C_{23}H_{31}N_3O_4$: C 66.81, H 7.56, N 10.16, found: C 66.48, H 7.50, N 10.10.

4.6.2. 2,3-Dihydro-1′-[4-(8-azaspiro[4,5]decane-7,9-dione)butyl]spiro(1,4-dioxino[2,3-*b*]pyridine)-2,3′-pyrrolidine 12B. Oil; IR (film) ν 1720 and 1640 (NCO), 1275 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40–1.76 (m, 12H, H_1, H_2, H_3, H_4, N–CH_2–(CH_2)$_2$–CH_2–N), 2.00–2.23 (m, 2H, CH_2–CH_2–N), 2.57 (s, 4H, H_6, H_{10}), 2.62–2.75 (m, 2H, CH_2–CH_2–N), 3.25–3.70 (m, 6H, C–CH_2–N, N–CH_2–(CH_2)$_3$–N, CH_2–N–CO), 4.11 (d, 1H, J=11.3 Hz, O–CH_2–C), 4.33 (d, 1H, J=11.3 Hz, O–CH_2–C), 6.89 (dd, 1H, J=4.5, 7.8 Hz, H_β), 7.21 (dd, 1H, J=1.5, 7.8 Hz, H_γ), 7.84 (dd, 1H, J=1.5, 4.5 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 24.1 (CH_2), 24.6 (CH_2), 25.9 (CH_2), 27.8 (CH_2), 31.1 (CH_2), 37.3 (CH_2), 39.1 (C), 39.2 (CH_2), 44.6 (CH_2), 48.7 (CH_2), 58.3 (CH_2), 71.1 (CH_2), 72.1 (C), 118.4 (CH), 124.6 (CH), 138.2 (CH), 139.9 (C), 149.9 (C), 172.1 (CO); MS (CI) *m*/*z* 414 (M+1); Anal. calcd for $C_{23}H_{31}N_3O_4$: C 66.81, H 7.56, N 10.16, found: C 66.51, H 7.45, N 10.21.

4.6.3. 2,3-Dihydro-1′-[4-(8-azaspiro[4,5]decane-7,9-dione)butyl]spiro(1,4-dioxino[2,3-*b*]pyridine)-3,4′-piperidine 13A. Oil; IR (film) ν 1710 and 1640 (NCO), 1280 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35–1.60 (m, 8H, H_1, H_2, H_3, H_4), 1.61–1.84 (m, CH_2–CH_2–N, N–CH_2–(CH_2)$_2$–CH_2–N), 2.30–2.47 (m, 4H, CH_2–CH_2–N), 2.55 (s, 4H, H_6, H_{10}), 2.63–2.70 (m, 2H, N–CH_2–(CH_2)$_3$–N), 3.71 (t, 2H, J=6.6 Hz, CH_2–N–CO), 4.05 (s, 2H, O–CH_2–C), 6.86 (dd, 1H, J=4.7, 7.8 Hz, H_β), 7.15 (dd, 1H, J=1.6, 7.8 Hz, Hγ), 7.77 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_2), 25.2 (CH_2), 26.1 (CH_2), 31.0 (CH_2), 37.5 (CH_2), 39.3 (C), 39.5 (CH_2), 44.9 (CH_2), 48.4 (CH_2), 58.0 (CH_2), 71.4 (CH_2), 71.7 (C), 118.7 (CH), 125.0 (CH), 137.4 (CH), 140.0 (C), 150.4 (C), 172.2 (CO); MS (CI) *m*/*z* 428 (M+1); Anal. calcd for $C_{24}H_{33}N_3O_4$: C 67.42, H 7.78, N 9.83, found: C 67.73, H 7.67, N 10.12.

4.6.4. 2,3-Dihydro-1′-[4-(8-azaspiro[4,5]decane-7,9-dione)butyl]spiro(1,4-dioxino[2,3-*b*]pyridine)-2,4′-piperidine 13B. Oil; IR (film) ν 1720 and 1660 (NCO), 1267 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–1.57 (m, 8H, H_1, H_2, H_3, H_4), 1.60–1.84 (m, CH_2–CH_2–N, N–CH_2–(CH_2)$_2$–CH_2–N), 2.33–2.48 (m, 4H, CH_2–CH_2–N), 2.53 (s, 4H, H_6, H_{10}), 2.60–2.71 (m, 2H, N–CH_2–(CH_2)$_3$–N), 3.72 (t, 2H, J=6.6 Hz, CH_2–N–CO), 4.13 (s, 2H, O–CH_2–C), 6.84 (dd, 1H, J=4.8, 7.8 Hz, H_β), 7.15 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.77 (dd, 1H, J=1.6, 4.8 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 24.2 (CH_2), 25.2 (CH_2), 26.0 (CH_2), 31.1 (CH_2), 37.5 (CH_2), 39.2 (C), 39.5 (CH_2), 44.9 (CH_2), 48.5 (CH_2), 58.0 (CH_2), 71.5 (CH_2), 71.6 (C), 118.7 (CH), 125.1 (CH), 137.5 (CH), 139.5 (C), 150.4 (C), 172.2 (CO); MS (CI) *m*/*z* 428 (M+1); Anal. calcd for $C_{24}H_{33}N_3O_4$: C 67.42, H 7.78, N 9.83, found: C 67.68, H 7.76, N 10.01.

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