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Tetrahedron 60 (2004) 6461–6473
Tetrahedron

Efficient synthesis of 2- and 3-substituted-2,3-dihydro [1,4]dioxino[2,3-*b*]pyridine derivatives

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Received 7 April 2004; revised 1 June 2004; accepted 8 June 2004

Abstract—A versatile new approach for the synthesis in three steps of 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **B** via a Smiles rearrangement using easily available reagents is described. A study illustrating the influence of experimental conditions on the progress of the reaction is reported.

1. Introduction

The 2,3-dihydro[1,4]benzodioxin ring constitutes an important skeletal fragment in medicinal chemistry and hence, a variety of reports have been presented for their synthesis and biological evaluation of compounds including this ring.[1] Some of them are antagonists of α-adrenergic receptors, with antihypertensive properties.[2–6] Other have affinities for serotonin receptors involved in nervous breakdown and schizophrenia[7–12] or represent an attractive therapeutic target for the treatment of glaucoma.[13] Moreover, they showed additional interesting properties used for the treatment and prevention of atherosclerosis and oxidative injuries.[14] Recently, 2,3-dihydro[1,4]benzodioxins have been developed as inhibitors of 5-lipoxygenase, an enzyme involved in the oxygenation of arachidonic acid to the leukotriens. They are also useful for the treatment of inflammatory diseases such as asthma and arthritis.[15] The occurrence of the 2,3-dihydro[1,4]-benzodioxin structure in various naturally abundant compounds has been already reported.[16,17]

In connection with the development of new potential 5-HT_{1A} ligands, we are interested in the study of the 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine skeleton. To the best of our knowledge, only this polyheterocyclic system has been prepared by treatment of 3-hydroxy-2-pyridone with base and 1,2-dibromoethane.[18] This method, unfortunately too restrictive, not only gives unsatisfactory yield but also makes the introduction of various substituents in the six-membered non aromatic moiety infeasible.

Previously, we have reported the synthesis of 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine derivatives functionalized at the oxygenated moiety in position 3 (**A** in Fig. 1).[19] Compounds **B** (Fig. 1) substituted in position 2 were mentioned only once and are obtained by a relatively long synthesis implementing starting materials such as the 2-chloro-3-pyridinol and the 1-acetoxy-3-benzyloxy-2-propanol.[20] In addition, E. Matesanz et al. have recently described a new strategy for the synthesis of 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine and 7-substituted-6,7-dihydro-[1,4]dioxino[2,3-*d*]pyrimidine developed as potential new therapeutic agents.[21]

Figure 1.

In continuation of our research program concerning the dioxinopyridines, we have reported a convenient effective synthetic pathway to 2-substituted-2,3-dihydro-[1,4]-dioxino[2,3-*b*]pyridines **B**[22] via a Smiles rearrangement.[23] A similar approach was developed by Y. J. Yoon et al. for the synthesis of pyrido[2,3-*b*][1,4]oxazin-2-ones by one-pot

Keywords: 2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridine; Smiles rearrangement; Nucleophilic aromatic substitution.
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doi:10.1016/j.tet.2004.06.041

annulation of *N*-substituted-2-chloroacetamides with 2-halo-3-hydroxypyridines.[24] In addition, we recently described a practical and effective synthetic route to isomeric 2- and 3-substituted-2,3-dihydro-spiro[1,4]-dioxino[2,3-*b*]pyridine amino derivatives, developed as potential 5-HT_{1A} ligands.[25] The present paper is focused on the extension of this preliminary work and on the study of the influence of experimental conditions (e.g., base, solvent, nucleofuge and substrate structure) on the progress of the Smiles rearrangement.

2. Results and discussion

Our strategy consists, first, in the formation of the epoxide **2a**–**f** and then on its opening by appropriate nucleophiles to the corresponding alcohols **3a**–**f**, **4b**, **4e**, **5b**, **5e**, **6b**, **6e**, **7b** and **7e**. Alcohols are the key intermediates for the synthesis of the target molecules.

Epoxides **2a**–**f**, prepared by treatment of pyridinol **1a**–**f** with excess epichlorohydrin using NaH in DMF, were used after purification for subsequent reactions with nucleophiles (Scheme 1). Given the diversity of the possible means of opening for an oxirane, it is possible to prepare compounds bearing diversified substituents on the oxygenated moiety.

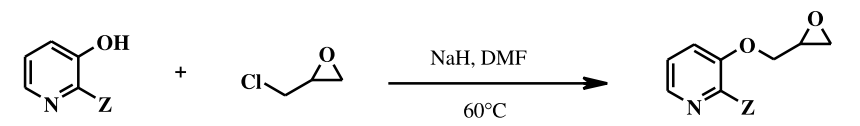
2.1. Preparation of the alcohols 3–6

Compounds containing an arylpiperazine moiety constitute a class of important agents with a variety of pharmacological activities.[26] Indeed, the ring opening of epoxide **2** with phenylpiperazine was promoted by use of THF at reflux, affording the corresponding amino alcohols **3a**–**f** in good yields (Scheme 2). The reaction was carried out with only 3 equiv. of amine.

A stirring slurry of activated commercially available Woelm 200 neutral chromatographic alumina (500 °C, 24 h) catalyzed the regioselective opening of epoxides **2b** and **2e** by benzyl alcohol under mild conditions (25 °C, THF)[27] to give the corresponding functionalized alcohols **4b** and **4e** in satisfactory yields (Scheme 3). The similar ring opening of epoxides **2b** and **2e** by *N*-methylbenzylamine or benzylamine at reflux of THF gave the corresponding amino alcohols **5b** and **5e** or **6b** and **6e** in good yields (Scheme 3). The synthesis of the azido alcohols **7b** and **7e** was achieved through the regioselectively opening of the epoxides **2b** and **2e** with sodium azide, in the presence of ammonium chloride[28] (Scheme 3).

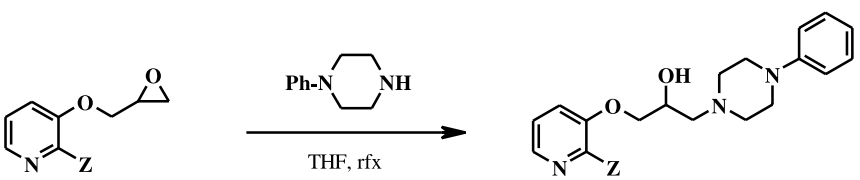
2.2. Cyclization reaction

The second part of the study concerned the cyclization of the alcohols **3**–**7** by intramolecular nucleophilic aromatic substitution (S_NAr) to afford the 3-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **A**[19d] (Scheme 4, pathway a). However, due to the selected experimental conditions (e.g., base, solvent, nucleofuge and substrate structure), 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]-pyridines **B** (Scheme 4, pathway b) have been isolated in fairly good yields. Formation of the isomers **B** could be explained by a Smiles rearrangement involving the attack of alkoxide on the 3-position of pyridine ring with displacement of the alkoxide, and the subsequent closure of the delivered alkoxide into the 2-position of pyridine ring.



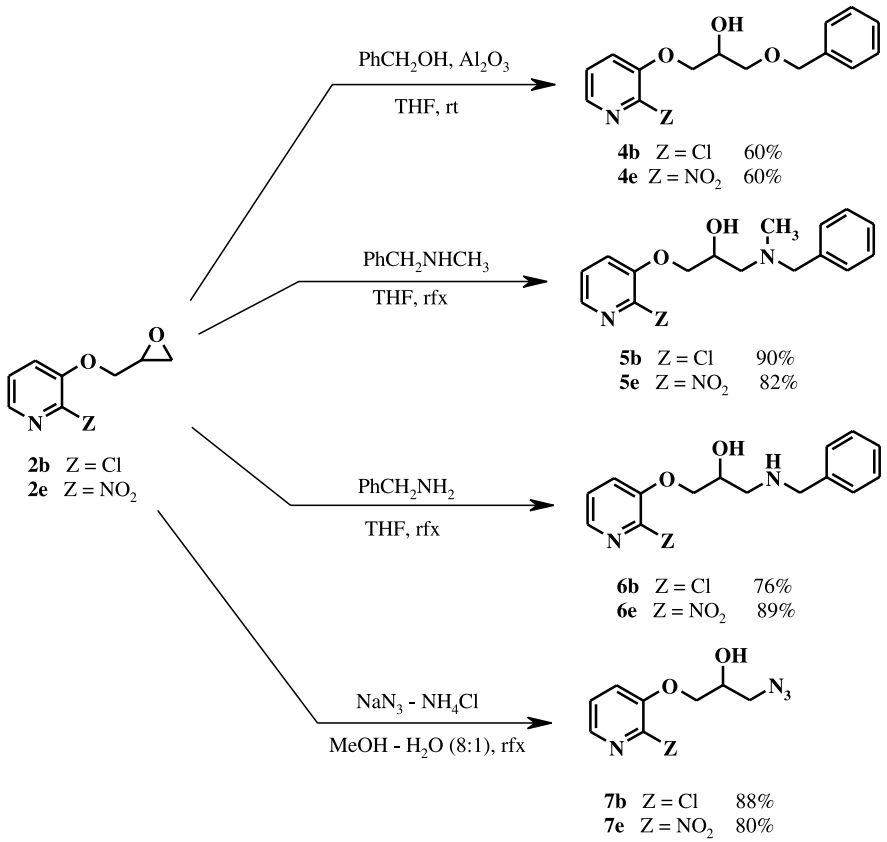
	1a	Z = F	**2a** Z = F 82%
	b	Z = Cl	**b** Z = Cl 85%
	c	Z = Br	**c** Z = Br 83%
a)	**d**	Z = I	**d** Z = I 75%
	e	$Z = NO_2$	**e** $Z = NO_2$ 81%
	f	Z = OMe	**f** Z = OMe 85%

Scheme 1. (a): (i) NaH, DMF, $PhCH_2Br$, rt; 91%. (ii) MeONa, DMF, 80 °C; 92%. (iii) H_2, Pd/C 10%, MeOH, rt; 85%.

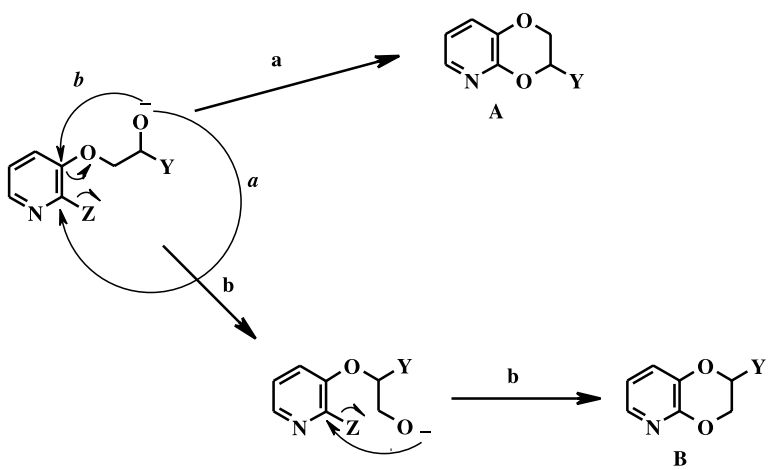


2a	Z = F	**3a**	Z = F 91%
b	Z = Cl	**b**	Z = Cl 95%
c	Z = Br	**c**	Z = Br 90%
d	Z = I	**d**	Z = I 85%
e	$Z = NO_2$	**e**	$Z = NO_2$ 88%
f	Z = OMe	**f**	Z = OMe 74%

Scheme 2.



Scheme 3.

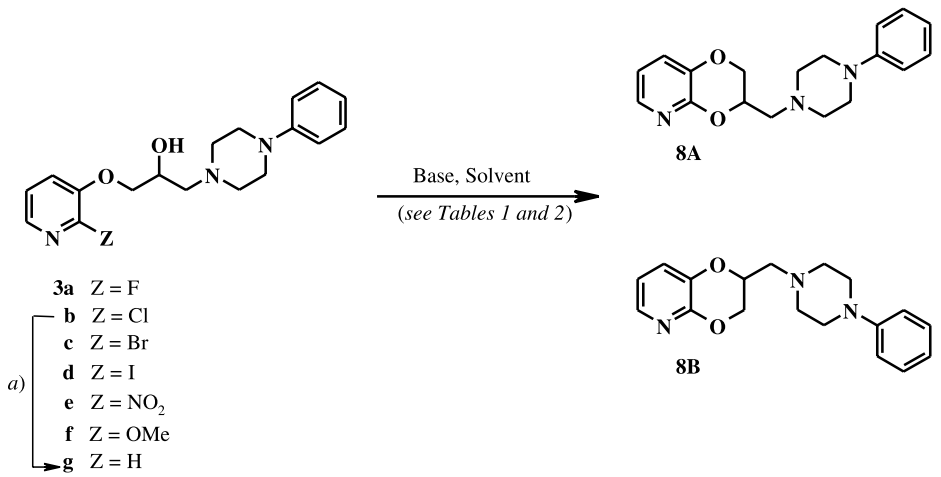


Scheme 4.

The two **A** and **B** isomers resulting from the cyclization of alcohols **3a**–**g** are presented in Scheme 5.

A study of conditions affecting this rearrangement was carried out by varying different parameters such as nucleofuge, base and solvent. The results obtained from the cyclization reaction of alcohols **3a**–**g** are summarized in Table 1.

The Smiles rearrangement is facilitated when the aromatic ring is activated by electron-withdrawing groups in the *ortho* position. In fact, after extensive optimization studies, we found that the use of the strong electron-withdrawing nitro group as leaving group increased the yield of rearranged product **B**. In the entry 5, whatever base and solvent conditions, it was found that the total yield of the intramolecular cyclization reaction is excellent, and consequently, the isomer **8B** was isolated as major product. These results are highly interesting because they afford an access to the isomer **B** in three steps starting from the pyridinols **1**. The isomers **8A** and **8B** were separated by flash chromatography and their structures were assigned mainly based on NMR (1D and 2D). Moreover, the structure of **8A**, as a racemic mixture, was confirmed by X-ray diffraction,



Scheme 5. (a): AcONa, Pd/C 10%, MeOH, rt, 12 h; 90%.

Table 1. Cyclization of compounds **3**

Entry	Z	Base/solvent	*T* (°C)	*t* (h)	Products **8** (yield %)[a]	
					A	**B**
1	F	NaH/DME	80	48	58	—
		t-BuOK/*t*-BuOH	80	48	50	7
2	Cl	NaH/DME	80	72	62	—
		t-BuOK/*t*-BuOH	80	72	45	15
3	Br	NaH/DME	80	48	67	—
		t-BuOK/*t*-BuOH	80	48	56	13
4	I	NaH/DME	80	48	65	8
		t-BuOK/*t*-BuOH	80	48	61	14
5	NO_2	NaH/DME	80	12	30	59
		t-BuOK/*t*-BuOH	80	12	44	52
6	OMe	NaH/DME	80	72	5[b]	—
7	H	NaH/DME	80	72	—[c]	—[c]

[a] Isolated yield of each isomer after separation by flash chromatography.
[b] The starting material was recovered in 78% yield.
[c] Only the starting material was recovered in 75% yield.

clearly identifying the substitution position on the dioxine ring (Fig. 2). In the solid state, the conformation of **8A** is quasi planar, with a dihedral angle O(15)–C(14)–C(13)–N(10)=−170.7(1)°. Bond lengths and angles do not show surprising features.

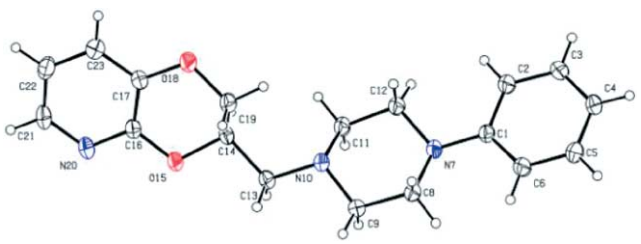


Figure 2. The ORTEP drawing of **8A** with thermal ellipsoids at 30% level.

After having shown the interest of the leaving group choice for the Smiles rearrangement pathway, we tested the feasibility of this rearrangement in absence of any leaving group. For this purpose, the corresponding **3g** alcohol was prepared from alcohol **3b** in the presence of AcONa, Pd/C in MeOH, in 90% yield. In this case, only the starting material without any trace of the rearranged compound was obtained by using the operating conditions described in Table 1, entry 7.

As can be seen from Table 1, the ratio of isomers **8A** and **B** varies also, with the nature of base and solvent. In entries 1–4, only one **A** isomer is obtained with the NaH/DME system, except with iodine ion, while similar low yields in rearranged product **B** are obtained with the *t*-BuOK/*t*-BuOH system (entries 2–4). Note also, when different counterions (Na^+, Li^+ and K^+) were tested, no particular influence was noticed concerning the formation of isomer **B** (Table 2).

Table 2. Effect of the counterion on the cyclization of the compound **3e**

Entry	Z	Base/solvent	*T* (°C)	*t* (h)	Products (yield %)	
					A	**B**
1	NO_2	NaH/DME	80	12	30	59
2	NO_2	LiH/DME	80	8	37	51
3	NO_2	KH/DME	80	4	34	50

In order to expand this study, on the basis of these results, we selected the alcohols **4**, **5**, **6** and **7** with chloro and nitro group as leaving groups to synthesize the corresponding **A** and **B** isomers. The desired products were obtained with satisfactory yields, by using the same conditions of cyclization reactions (Tables 3 and 4 and Scheme 6).

When NaH was used for deprotonation of chloro-alcohols **4b**, **6b** and **7b** (entries 1, 9 and 13, respectively), we obtained exclusively the **A** product from normal ring closure. However, a mixture of the **A** and **B** isomers was formed upon deprotonation by using *t*-BuOK in *t*-BuOH.

On the other hand, when *t*-BuOK/*t*-BuOH was used for deprotonation of **4b**, **5b** and **7b** (entries 2, 6 and 14, respectively) low yields of **B** were obtained, whereas only traces of **B** were observed from alcohol **6b** (entry 10).

Table 3. Cyclization of compounds **4**, **5** and **6**

Entry	Y	Z	Base/solvent	*T* (°C)/*t* (h)	Products (yield %)[a]	Ratio[b] (**A/B**)
1	OCH_2Ph	Cl	NaH/DME	80/72	65	100/0
2			*t*-BuOK/*t*-BuOH	80/72	60	70/30
3	OCH_2Ph	NO_2	NaH/DME	80/12	98	50/50
4			*t*-BuOK/*t*-BuOH	80/12	94	40/60
5	$N(CH_3)CH_2Ph$	Cl	NaH/DME	80/72	60	100/0
6			*t*-BuOK/*t*-BuOH	80/72	62	75/25
7	$N(CH_3)CH_2Ph$	NO_2	NaH/DME	80/12	88	70/30
8			*t*-BuOK/*t*-BuOH	80/12	89	30/70
9	$NHCH_2Ph$	Cl	NaH/DME	80/72	65	100/0
10			*t*-BuOK/*t*-BuOH	80/72	64	95/5
11	$NHCH_2Ph$	NO_2	NaH/DME	80/12	90	45/55
12			*t*-BuOK/*t*-BuOH	80/12	89	30/70

[a] Yields of cyclization reaction after flash chromatography.
[b] Ratio of each isomer determined by ^1H NMR.

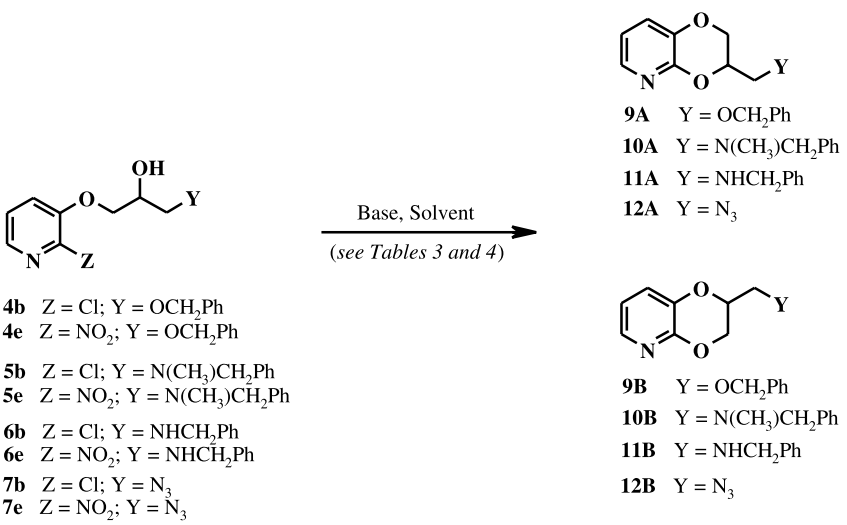
Table 4. Cyclization of compounds **7**

Entry	Y	Z	Base/solvent	*T* (°C)/*t* (h)	Products (yield %)[a]	
					A	**B**
13	N_3	Cl	NaH/DME	80/48	62	—
14			*t*-BuOK/*t*-BuOH	80/48	45	17
15	N_3	NO_2	NaH/DME	80/28	55	36
16			*t*-BuOK/*t*-BuOH	80/28	48	38

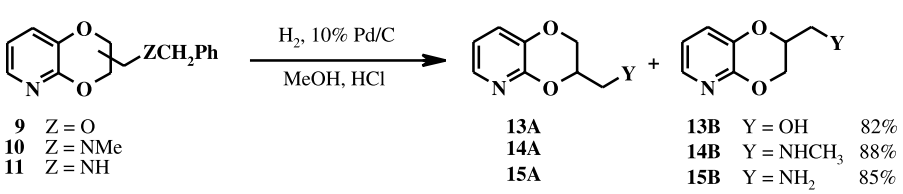
[a] Isolated yield after separation by flash chromatography.

Under similar cyclization reaction conditions the alcohols **4e**–**7e**, with a nitro leaving group, gave a mixture of the **A** and **B** isomers in various ratios (entries 3,7,11 and 15). Only isomers **12A** and **12B** were separated by column chromatography.

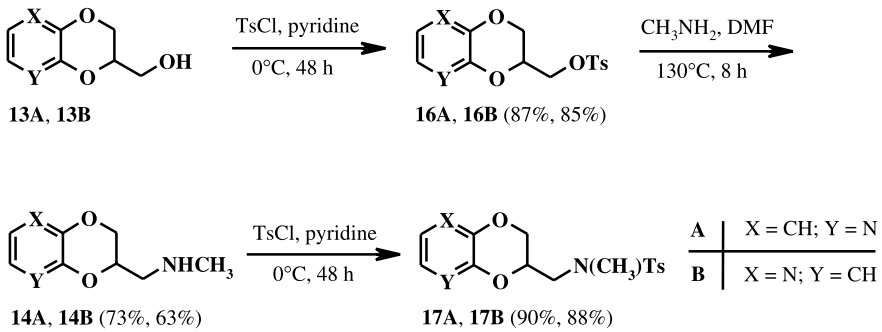
By analogy with results from a completed work in 2,3-dihydro[1,4]benzodioxin series,[12] it would be also necessary to have the aminomethyl or hydroxymethyl group in position 2 of the 2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine. Thus, catalytic Pd/C hydrogenolysis of compounds **9**, **10** and **11** in methanol with a few drops of concentrated hydrochloric acid gave debenzylated products **13**, **14** and **15** in good yields (Scheme 7).



Scheme 6.



Scheme 7.



Scheme 8.

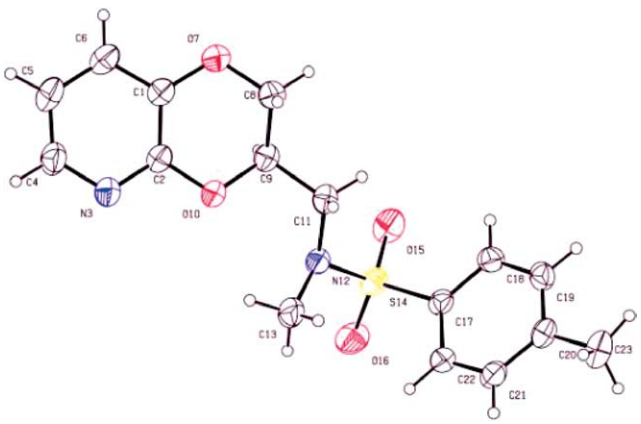


Figure 3. The ORTEP drawing of **17A** with thermal ellipsoids at 30% level.

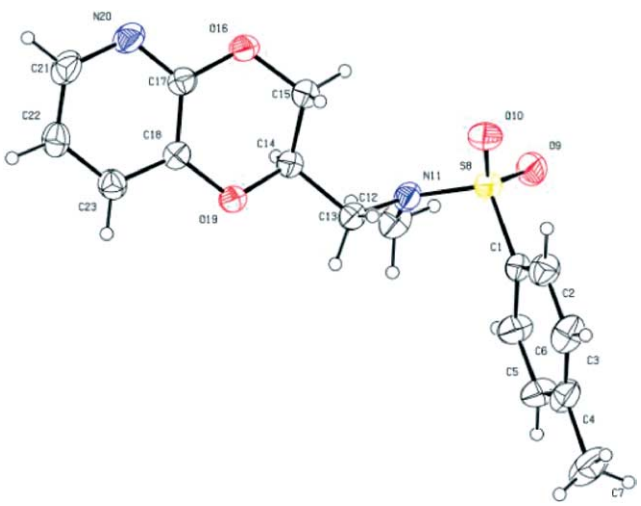


Figure 4. The ORTEP drawing of **17B** with thermal ellipsoids at 30% level.

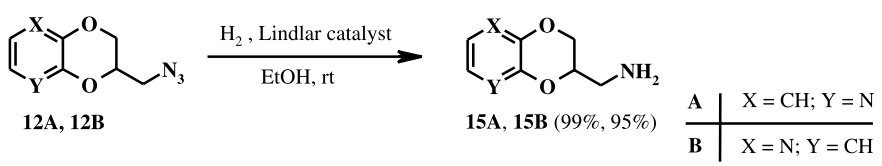
The isomeric mixtures (**13A**+**13B**), (**14A**+**14B**) and (**15A**+**15B**) were separated by column chromatography after debenzylation of compounds **9**, **10** and **11**, respectively.

By reaction with *p*-toluensulfonyl chloride in pyridine at 0 °C for 48 h the alcohols **13A** and **13B** afforded the expected derivatives **16A** and **16B** in excellent yields. Then, the nucleophilic replacement of the tosyl group with methylamine in DMF at 130 °C for 8 h produced the corresponding amines **14A** and **14B**.[29] Under similar sulfonation reaction conditions, the resulting amines **14A** and **14B** were converted into their sulfonated derivatives **17A** and **17B** in good yields (Scheme 8). The sulfonation reaction of the alcohols **13A** and **13B** and the *N*-methylamines **14A** and **14B** was realized to prove the structure of these isomers.

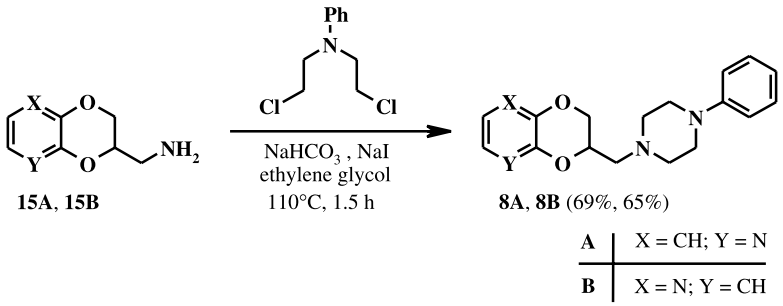
In order to formally establish the structure of these dioxinopyridine derivatives, an X-ray analysis was performed for **17A** and **17B**. ORTEP views of a single molecule of **17A** and **17B** are depicted in Figs. 3 and 4, respectively. In both cases, results confirmed the position of the lateral chain on the dioxine ring. In **17A** the C(9)–C(11) bond length is 1.524(5) Å, similar to the corresponding C(14)–C(13) bond length in **17B** [1.525(2) Å]. Fortuitously, the **17A** crystal used for the X-ray study is one enantiomer, as indicated by the spatial group ($P2_1$). The main conformational difference between **17A** and **17B** concerns the corresponding O(10)–C(9)–C(11)–N(12) and O(19)–C(14)–C(13)–N(11) dihedral angles, found at 59.9(2)° for **17A** and −164.7(2)° for **17B**, respectively. On the other hand, bond lengths and angles do not show surprising features. The X-ray data of **17A** and **17B** confirmed indirectly the structure of the alcohols **13A** and **13B** and the *N*-methylamines **14A** and **14B**.

As *N*-alkylated compounds are susceptible to present interesting biological proprieties, we decided to regenerate the free primary 2-(2,3-dihydro[1,4]-dioxino[2,3-*b*]pyridine)ylmethylamines **15A** and **15B**. Hence, the direct conversion of compounds **12** into the corresponding amines **15** was achieved by catalytic hydrogenation (Scheme 9).

These free amines **15A** and **15B** offer many possibilities for



Scheme 9.



Scheme 10.

further reactions. For example, the direct alkylation of these amines, with *N,N*-bis(2-chloroethyl)aniline in the presence of sodium hydrogen carbonate and sodium iodide in ethylene glycol afforded the expected dioxinopyridine derivatives **8A** and **8B** in 69%, 65% yields, respectively (Scheme 10). Moreover, this sequence allows to confirm the structures of **12A**, **12B**, and also of **15A**, **15B**.

3. Conclusion

In summary, using easily available reagents, we have developed a convenient strategy that gave access in satisfactory yields to the corresponding 2- and 3-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines (**A** and **B**). In comparison with classical synthesis of 3-substituted derivatives **A** by nucleophilic aromatic substitution (S_NAr), the access to 2-substituted-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridines **B** was realized in three steps via a Smiles rearrangement. By studying the influence of experimental conditions on the progress of the reaction we observed that the Smiles rearrangement is facilitated by activation of the aromatic ring by electron-withdrawing groups in the *ortho* position, for example, the use of the strong electron-withdrawing nitro group as leaving group increased the yield of rearranged product **B**. The functionalisation of these compounds in 2 or 3 position with aminomethyl or hydroxymethyl groups could be of potential utility for further developments in medicinal chemistry.

4. Experimental

Melting points were determined in capillary tubes with Büchi SMP-20 or on a Köfler apparatus and are uncorrected. IR spectra were obtained on Perkin–Elmer Paragon 1000 PC FT-IR. ^1H and ^{13}C NMR spectra were, respectively, recorded at 250 and 62.9 MHz on Bruker Avance DPX250. Chemical shifts (δ values) were reported in ppm and coupling constants (J values) in Hz. Me_4Si was the internal standard. Elemental analyses were performed by CNRS laboratory (Vernaison, France). Microanalyses for the elements indicated were within 0.3% of theoretical values. MS data were taken on a Perkin–Elmer SCIEX type API 300. 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. Commercial reagents were used as received without additional purification. All reactions involving moisture-sensitive reagents were performed under an argon atmosphere. All organic solvents were distilled immediately prior to use, and magnesium sulfate was used for drying solutions of organic solvents.

The crystal structures of **8A**, **17A** and **17B** have been determined by single-crystal X-ray diffraction techniques. Diffraction data were collected using a CAD4 Enraf–Nonius diffractometer with graphite monochromatized Cu Kα radiation. The cell parameters were determined by least-squares from the setting angles for 25 reflexions. An empirical absorption correction was applied. The data were also corrected for Lorentz and polarization effect. The positions of non-H atoms were determined by the program SHELXS 86[30] and the position of the H atoms were included for structure factor calculations but not refined.

For **8A**, the crystal is monoclinic, space group $P2_1/n$, with a=7.414(10) Å, b=7.005(4) Å, c=30.370(4) Å, β=90.94(1)°, and Z=4. A crystal 0.15×0.50×0.60 was chosen. For **17A**, the crystal is monoclinic, space group $P2_1$, with a=8.107(1) Å, b=6.179(1) Å, c=15.753(1) Å, β=92.74(1)°, and Z=2. A crystal 0.37×0.20×0.12 mm was chosen. For **17B**, the crystal is monoclinic, space group $P2_1/c$ with a=19.653(4) Å, b=5.828(1) Å, c=15.069(2) Å, β=112.33(2)°, and Z=4. A crystal 0.37×0.25×0.12 mm was chosen.

The X-ray results confirm the structure as anticipated on the basis of ^{13}C and ^1H NMR data. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Center (CCDC), UK, as Supplementary Materials.[31]

4.1. General procedure for the preparation of the epoxides 2a–f

To a stirred suspension of NaH (5.33 g of 60% oil dispersion, 158.60 mmol) in DMF (50 mL) was added dropwise a solution of appropriate pyridinol **1a–f** (132 mmol) in DMF (50 mL). After 45 min, a solution of epichlorohydrin (103.5 mL, 1.32 mol) in DMF (25 mL) was added and the mixture was stirred at 60 °C during 72 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: AcOEt/petroleum ether, 1:1) to give the corresponding epoxides **2a–f**.

4.1.1. 2-Fluoro-3-oxiranylmethoxypyridine 2a. Oil; IR (film) ν 1289 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78

(dd, 1H, J=2.6, 4.8 Hz, Ar-O–CH_2–CH–CH_2), 2.93 (t, 1H, J=4.8 Hz, Ar-O–CH_2–CH–CH_2), 3.34–3.43 (m, 1H, CH_2–CH–CH_2), 4.00 (dd, 1H, J=6.1, 11.4 Hz, Ar-O–CH_2), 4.40 (dd, 1H, J=2.6, 11.4 Hz, Ar-O–CH_2), 7.14 (ddd, 1H, J=0.8, 4.9, 7.9 Hz, H_β), 7.33–7.45 (m, 1H, H_γ), 7.76 (dt, 1H, J=3.2, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.1, 50.1, 71.2, 118.0, 124.6, 142.2, 142.3, 153.9; MS (CI) m/z 170 (M+1); Anal. calcd for $C_8H_8FNO_2$: C, 56.80; H, 4.77; N, 8.28. Found: C, 56.91; H, 4.80; N, 8.39.

4.1.2. 2-Chloro-3-oxiranylmethoxypyridine 2b. Mp 35–36 °C; IR (KBr) ν 1280 and 1200 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.83 (dd, 1H, J=2.7, 4.9 Hz, Ar-O–CH_2–CH–CH_2), 2.94 (t, 1H, J=4.9 Hz, Ar-O–CH_2–CH–CH_2), 3.36–3.44 (m, 1H, CH_2–CH–CH_2), 4.04 (dd, 1H, J=5.4, 11.4 Hz, Ar-O–CH_2), 4.39 (dd, 1H, J=2.8, 11.3 Hz, Ar-O–CH_2), 7.20 (dd, 1H, J=4.7, 8.2 Hz, H_β), 7.30 (dd, 1H, 1.6, 8.2 Hz, H_γ), 8.01 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ NMR ($CDCl_3$) δ 44.1, 49.7, 69.5, 120.8, 123.2, 140.8, 141.0, 150.5; MS (CI) m/z 186 (M+1); Anal. calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.81; H, 4.42; N, 7.69.

4.1.3. 2-Bromo-3-oxiranylmethoxypyridine 2c. Mp 50–51 °C; IR (KBr) ν 1294 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (dd, 1H, J=2.7, 4.9 Hz, Ar-O–CH_2–CH–CH_2), 2.86 (t, 1H, J=4.9 Hz, Ar-O–CH_2–CH–CH_2), 3.28–3.37 (m, 1H, CH_2–CH–CH_2), 3.96 (dd, 1H, J=5.5, 11.4 Hz, Ar-O–CH_2), 4.33 (dd, 1H, J=2.7, 11.4 Hz, Ar-O–CH_2), 7.10–7.19 (m, 2H, H_β, H_γ), 7.92 (dd, 1H, J=2.7, 3.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.3, 49.8, 69.6, 120.4, 123.5, 132.9, 141.8, 151.9; MS (CI) m/z 230 (M+1 for ^{79}Br) and 232 (M+1 for ^{81}Br); Anal. calcd for $C_8H_8BrNO_2$: C, 41.77; H, 3.51; N, 6.09. Found: C, 41.91; H, 3.60; N, 6.15.

4.1.4. 2-Iodo-3-oxiranylmethoxypyridine 2d. Oil; IR (film) ν 1285 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.79–2.88 (m, 2H, Ar-O–CH_2–CH–CH_2), 3.27–3.37 (m, 1H, CH_2–CH–CH_2), 3.95 (dd, 1H, J=5.3, 11.4 Hz, Ar-O–CH_2), 4.32 (dd, 1H, J=2.4, 11.4 Hz, Ar-O–CH_2), 7.00 (dd, 1H, J=1.6, 8.2 Hz, H_γ), 7.11 (dd, 1H, J=4.6, 8.2 Hz, H_β), 7.91 (dd, 1H, J=1.6, 4.6 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.2, 49.6, 69.3, 111.7, 118.5, 123.5, 142.8, 153.9; MS (CI) m/z 278 (M+1); Anal. calcd for $C_8H_8INO_2$: C, 34.68; H, 2.91; N, 5.06. Found: C, 34.72; H, 3.03; N, 5.19.

4.1.5. 2-Nitro-3-oxiranylmethoxypyridine 2e. Mp 52–53 °C; IR (KBr) ν 1256 and 1170 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.79 (dd, 1H, J=2.8, 4.6 Hz, Ar-O–CH_2–CH–CH_2), 2.91 (t, 1H, J=4.6 Hz, Ar-O–CH_2–CH–CH_2), 3.31–3.41 (m, 1H, CH_2–CH–CH_2), 4.10 (dd, 1H, J=5.6, 11.6 Hz, Ar-O–CH_2), 4.49 (dd, 1H, J=2.5, 11.6 Hz, Ar-O–CH_2), 7.52 (dd, 1H, J=4.4, 8.5 Hz, H_β), 7.62 (dd, 1H, 1.3, 8.5 Hz, H_γ), 8.09 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.4, 49.8, 70.4, 124.6, 128.8, 140.0, 146.9; MS (CI) m/z 197 (M+1); Anal. calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.11; H, 4.23; N, 14.39.

4.1.6. 2-Methoxy-3-oxiranylmethoxypyridine 2f. Mp 31–32 °C; IR (KBr) ν 1283 and 1197 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.68 (dd, 1H, J=2.6, 4.8 Hz, Ar-O–CH_2–CH–CH_2), 2.84 (t, 1H, J=4.8 Hz, Ar-O–CH_2–CH–CH_2), 3.27–3.35 (m, 1H, CH_2–CH–CH_2), 3.88–3.98 (m, 4H, Ar-O–CH_2, CH_3), 4.22 (dd, 1H, J=3.1, 11.3 Hz, Ar-O–CH_2), 6.76 (dd, 1H, J=5.0, 7.8 Hz, H_β), 7.07 (dd, 1H, J=1.6, 7.8 Hz H_γ), 7.70 (dd, 1H, J=1.6, 5.0 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 44.7, 50.0, 53.5, 69.9, 116.7, 119.9, 138.1, 143.0, 154.8; MS (CI) m/z 182 (M+1); Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.71; H, 6.30; N, 7.79.

4.2. General procedure for the preparation of the alcohols 3a–f

To a solution of appropriate epoxides **2a–f** (6.73 mmol) in THF (30 mL) was added 1-phenylpiperazine (20 mmol). The mixture was stirred at reflux for 24 h then diluted with H_2O, extracted with AcOEt, dried over $MgSO_4$ and the solvent removed in vacuo to give the crude product. This was purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford the corresponding alcohols **3a–f**.

4.2.1. 1-(2-Fluoropyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3a. Oil; IR (film) ν 3500–3200 (OH), 1286 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49–2.68 (m, 4H, CH_2–N(CH_2)$_2$), 2.72–2.84 (m, 2H, CH–CH_2–N), 3.10–3.24 (m, 4H, Ph-N(CH_2)$_2$), 3.98–4.20 (m, 4H, O–CH_2–CH–OH), 6.77–6.95 (m, 3H, H_γ, H_{Ar}), 7.07 (ddd, 1H, J=0.8, 4.9, 7.8 Hz, H_β), 7.17–7.38 (m, 3H, H_{ar}), 7.71 (dd, 1H, J=1.7, 4.9 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.0, 53.2, 60.1, 65.5, 71.5, 115.9, 119.7, 122.4, 124.4, 129.1, 141.8, 142.2, 151.0, 154.0; MS (CI) m/z 332 (M+1); Anal. calcd for $C_{18}H_{22}FN_3O_2$: C, 65.24; H, 6.69; N, 12.68. Found: C, 65.33; H, 6.80; N, 12.76.

4.2.2. 1-(2-Chloropyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3b. Mp 107–108 °C; IR (KBr) ν 3500–3200 (OH), 1284 and 1209 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.58–2.73 (m, 4H, CH_2–N(CH_2)$_2$), 2.79–2.91 (m, 2H, CH–CH_2–N), 3.17–3.28 (m, 4H, Ph-N(CH_2)$_2$), 4.06–4.24 (m, 4H, O–CH_2–CH–OH), 6.81–6.96 (m, 3H, H_γ, H_{Ar}), 7.19 (dd, 1H, J=4.7, 8.1 Hz, H_β), 7.23–7.32 (m, 3H, H_{ar}), 8.00 (dd, 1H, J=1.5, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.4, 53.5, 60.4, 65.7, 71.5, 116.3, 120.1, 120.9, 123.3, 129.3, 141.1, 151.2, 151.3; MS (CI) m/z 348 (M+1); Anal. calcd for $C_{18}H_{22}ClN_3O_2$: C, 62.15; H, 6.38; N, 12.08. Found: C, 62.33; H, 6.45; N, 12.16.

4.2.3. 1-(2-Bromopyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3c. Mp 84–85 °C; IR (KBr) ν 3500–3200 (OH), 1291 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53–2.70 (m, 4H, CH_2–N(CH_2)$_2$), 2.72–2.85 (m, 2H, CH–CH_2–N), 3.08–3.25 (m, 4H, Ph-N(CH_2)$_2$), 3.98–4.22 (m, 4H, O–CH_2–CH–OH), 6.78–6.95 (m, 3H, H_β, H_{Ar}), 7.11–7.30 (m, 4H, H_γ, H_{ar}), 7.94 (dd, 1H, J=1.4, 4.8 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.1, 53.3, 60.3, 65.5, 71.4, 116.0, 119.7, 120.1, 123.4, 129.0, 132.9, 141.5, 151.0, 152.1; MS (CI) m/z 392 (M+1 for ^{79}Br) and 394 (M+1 for ^{81}Br); Anal. calcd for $C_{18}H_{22}BrN_3O_2$: C, 55.11; H, 5.65; N, 10.71. Found: C, 55.23; H, 5.80; N, 10.76.

4.2.4. 1-(2-Iodopyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3d. Mp 93–94 °C; IR (KBr) ν 3500–3200 (OH), 1284 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60–2.79 (m, 4H, CH_2–N(CH_2)$_2$), 2.81–2.94 (m, 2H, CH–CH_2–N), 3.16–3.35 (m, 4H, Ph-N(CH_2)$_2$), 4.05–4.26 (m,

4H, O–CH_2–CH–OH), 6.83–6.98 (m, 3H, H_β, H_{Ar}), 7.03–7.10 (m, 1H, H_γ), 7.16–7.32 (m, 3H, H_{ar}), 7.94 (dd, 1H, J=1.2, 5.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.3, 53.5, 60.5, 65.7, 71.5, 112.4, 116.2, 118.4, 120.0, 123.6, 129.2, 143.1, 151.2, 154.5; MS (CI) m/z 440 (M+1); Anal. calcd for $C_{18}H_{22}IN_3O_2$: C, 49.21; H, 5.05; N, 9.57. Found: C, 49.19; H, 5.11; N, 9.47.

4.2.5. 1-(2-Nitropyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3e. Mp 102–103 °C; IR (KBr) ν 3500–3200 (OH), 1537 (NO_2), 1275 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49–2.70 (m, 4H, CH_2–N(CH_2)$_2$), 2.72–2.85 (m, 2H, CH–CH_2–N), 3.10–3.25 (m, 4H, Ph-N(CH_2)$_2$), 4.08–4.30 (m, 4H, O–CH_2–CH–OH), 6.79–6.98 (m, 3H, H_{Ar}), 7.18–7.35 (m, 2H, H_{ar}), 7.50 (dd, 1H, J=4.4, 8.5 Hz, H_β), 7.60 (dd, 1H, J=1.3, 8.5 Hz, H_γ), 8.05 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 48.9, 53.1, 59.8, 65.4, 71.7, 115.9, 119.6, 124.3, 128.8, 128.9, 139.2, 147.2, 148.4, 150.9; MS (CI) m/z 359 (M+1); Anal. calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.23; H, 6.27; N, 15.56.

4.2.6. 1-(2-Methoxypyridin-3-yloxy)-3-(4-phenylpiperazin-1-yl)-propan-2-ol 3f. Oil; IR (film) ν 3500–3100 (OH), 1260 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50–2.68 (m, 4H, CH_2–N(CH_2)$_2$), 2.70–2.84 (m, 2H, CH–CH_2–N), 3.08–3.30 (m, 4H, Ph-N(CH_2)$_2$), 3.94–4.26 (m, 4H, O–CH_2–CH–OH), 6.75–6.98 (m, 4H, H_β, H_{Ar}), 7.05–7.15 (m, 1H, H_γ), 7.19–7.35 (m, 2H, H_{ar}), 7.75 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.0, 53.2, 53.3, 60.4, 71.5, 115.9, 116.6, 119.5, 119.6, 130.0, 137.6, 143.2, 151.0, 154.7; MS (CI) m/z 344 (M+1); Anal. calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.53; H, 7.40; N, 12.16.

4.3. Preparation of the alcohols 4

Epoxide **2b** or **2e** (5.38 mmol) was allowed to react in THF (50 mL) with 34 g of Woelm-200-neutral dehydrated alumina (500 °C, 24 h) doped with benzyl alcohol (5.6 mL, 53.80 mmol) for 1.5 h at room temperature. After the appropriate amount of time had elapsed, the slurry was filtered through a sintered glass funnel containing a Celite pad, and the collected alumina was washed with additional MeOH. The combined washings were concentrated, and the residue was purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to leave the alcohol **4b** (60%) or **4e** (60%).

4.3.1. 1-Benzyloxy-3-(2-chloropyridin-3-yloxy)-propan-2-ol 4b. Oil; IR (film) ν 3500–3200 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (d, 2H, J=5.6 Hz, Ph-CH_2–O–CH_2), 4.08–4.33 (m, 4H, Ar-O–CH_2–CH–OH), 4.58 (s, 2H, Ph-CH_2), 7.15–7.38 (m, 7H, H_β, H_γ, H_{Ar}), 8.00 (dd, 1H, J=1.9, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 68.9, 70.2, 70.6, 73.7, 120.8, 123.3, 127.9, 128.0, 128.6, 137.7, 141.0, 141.1, 150.9; MS (CI) m/z 294 (M+1); Anal. calcd for $C_{15}H_{16}ClNO_3$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.41; H, 5.40; N, 4.67.

4.3.2. 1-Benzyloxy-3-(2-nitropyridin-3-yloxy)-propan-2-ol 4e. Mp 74–75 °C; IR (KBr) ν 3500–3200 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (d, 2H, J=4.7 Hz, Ph-CH_2–O–CH_2), 4.06–4.26 (m, 4H, Ar-O–CH_2–CH–OH), 4.51 (s, 2H, Ph-CH_2), 7.20–7.35 (m, 5H, H_{ar}), 7.47 (dd, 1H, J=4.1, 8.4 Hz, H_β), 7.52 (dd, 1H, J=1.6, 8.4 Hz, H_γ), 8.03 (dd, 1H, J=1.6, 4.1 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 68.5, 70.3, 70.7, 73.5, 124.3, 127.8, 127.9, 128.4, 129.0, 137.6, 139.4, 147.2, 148.5; MS (CI) m/z 305 (M+1); Anal. calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.17; H, 5.42; N, 9.19.

4.4. Preparation of the amino alcohols 5 and 6

Following the procedure described for **3a**–**f** but substituting 1-phenylpiperazine by (20 mmol) of *N*-methylbenzylamine or benzylamine, the epoxide **2b** and **2e** gave the corresponding amino alcohol **5b** (90%), **5e** (82%), **6b** (76%) or **6e** (89%).

4.4.1. 1-(*N*-Benzyl-*N*-methylamino)-3-(2-chloropyridin-3-yloxy)-propan-2-ol 5b. Oil; IR (film) ν 3500–3200 (OH), 1291 and 1207 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 2.58 (dd, 1H, J=4.4, 12.2 Hz, CH–CH_2–N), 2.70 (dd, 1H, J=9.1, 12.2 Hz, CH–CH_2–N), 3.53 (d, 1H, J=12.9 Hz, O–CH_2–CH), 3.69 (d, 1H, J=12.9 Hz, O–CH_2–CH), 4.00–4.06 (m, 2H, CH_2-Ph), 4.08–4.20 (m, 2H, CH–OH), 7.11–7.40 (m, 7H, H_β, H_γ, H_{ar}), 7.98 (dt, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 42.5, 59.2, 62.6, 66.1, 71.4, 120.7, 123.2, 127.4, 128.4, 129.1, 138.2, 140.8, 141.2, 151.1; MS (CI) m/z 307 (M+1); Anal. calcd for $C_{16}H_{19}ClN_2O_2$: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.53; H, 6.30; N, 9.16.

4.4.2. 1-(*N*-Benzyl-*N*-methylamino)-3-(2-nitropyridin-3-yloxy)-propan-2-ol 5e. Oil; IR (film) ν 3500–3200 (OH), 1280 and 1190 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, CH_3), 2.52 (dd, 1H, J=4.7, 12.5 Hz, CH–CH_2–N), 2.63 (dd, 1H, J=8.0, 12.5 Hz, CH–CH_2–N), 3.50 (d, 1H, J=13.0 Hz, O–CH_2–CH), 3.61 (d, 1H, J=13.0 Hz, O–CH_2–CH), 4.01–4.20 (m, 4H, CH_2-Ph, CH–OH), 7.16–7.33 (m, 5H, H_{ar}), 7.48 (dd, 1H, J=4.4, 8.4 Hz, H_β), 7.57 (dd, 1H, 1.3, 8.4 Hz, H_γ), 8.02 (dd, 1H, J=1.3, 4.4 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 42.2, 58.8, 62.3, 66.0, 71.8, 124.3, 127.1, 128.2, 128.8, 128.9, 138.0, 139.1, 147.2, 148.4; MS (CI) m/z 318 (M+1); Anal. calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.53; H, 6.00; N, 13.36.

4.4.3. 1-(*N*-Benzylamino)-3-(2-chloropyridin-3-yloxy)-propan-2-ol 6b. Mp 65–66 °C; IR (KBr) ν 3600–3200 (OH, NH), 1285 and 1205 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.83 (dd, 1H, J=7.4, 12.1 Hz, CH–CH_2–N), 2.92 (dd, 1H, J=7.4, 12.1 Hz, CH–CH_2–N), 3.35 (broad s, 2H, OH, NH), 3.77–3.92 (m, 2H, O–CH_2–CH), 4.00–4.06 (m, 2H, CH_2-Ph), 4.09–4.19 (m, 2H, CH–OH), 7.11–7.20 (m, 2H, H_β, H_γ), 7.21–7.39 (m, 5H, H_{ar}), 7.98 (dd, 1H, J=2.0, 4.2 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 51.0, 53.7, 67.8, 71.9, 120.7, 123.3, 127.4, 128.4, 128.6, 139.2, 140.9, 141.0, 151.0; MS (CI) m/z 293 (M+1); Anal. calcd for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.62; H, 5.80; N, 9.76.

4.4.4. 1-(*N*-Benzylamino)-3-(2-nitropyridin-3-yloxy)-propan-2-ol 6e. Oil; IR (film) ν 3600–3200 (OH, NH), 1280 and 1210 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.76–2.94 (m, 4H, OH, NH, CH–CH_2–N), 3.83 (dd, 2H, J=13.4,

16.5 Hz, CH_2–Ph), 4.01–4.11 (m, 2H, CH–OH), 4.13–4.22 (m, 2H, O–CH_2–CH), 7.21–7.38 (m, 5H, H_{ar}), 2.92 (dd, 1H, J=7.4, 12.1 Hz, CH–CH_2–N), 3.35 (broad s, 2H, OH, NH), 7.52 (dd, 1H, J=4.1, 8.5 Hz, H_β), 7.57 (dd, 1H, J=1.7, 8.5 Hz, H_γ), 8.10 (dd, 1H, J=1.7, 4.1 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 50.8, 53.9, 67.9, 72.5, 124.3, 127.3, 128.3, 128.6 128.9, 139.7, 139.8, 147.5; MS (CI) m/z 304 (M+1); Anal. calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.49; H, 5.80; N, 13.76.

4.5. Preparation of the azido alcohols 7

A solution of epoxide **2b** or **2e** (10.76 mmol) in MeOH (42 mL) and H_2O (6 mL) was treated with NaN_3 (2.10 g, 32.40 mmol) and NH_4Cl (1.40 g, 25.80 mmol). The mixture was heated at reflux for 24 h, cooled and the solvent removed in vacuo. The residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was further extracted with AcOEt. The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo to give crude product. This was purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford the azido alcohol **7b** (88%) or **7e** (80%).

4.5.1. 1-Azido-3-(2-chloropyridin-3-yloxy)-propan-2-ol 7b. Oil; IR (film) ν 3400–3200 (OH), 2095 (N_3), 1280 and 1205 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.51–3.68 (m, 2H, Ar-O–CH_2), 4.10 (d, 2H, J=5.4 Hz, CH_2–N_3), 4.20–4.32 (m, 2H, CH–OH), 7.18–7.30 (m, 2H, H_β, H_γ), 8.02 (dd, 1H, J=2.0, 4.3 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 53.3, 68.9, 70.3, 121.0, 123.4, 141.0, 141.3, 150.7; MS (CI) m/z 229 (M+1); Anal. calcd for $C_8H_9ClN_4O_2$: C, 42.03; H, 3.97; N, 24.50. Found: C, 42.19; H, 3.80; N, 24.36.

4.5.2. 1-Azido-3-(2-nitropyridin-3-yloxy)-propan-2-ol 7e. Mp 77–78 °C; IR (KBr) ν 3400–3200 (OH), 2098 (N_3), 1265 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.25–3.44 (m, 2H, Ar-O–CH_2), 3.95–4.08 (m, 2H, CH–OH), 4.14–4.27 (m, 2H, CH_2–N_3), 7.75 (dd, 1H, J=4.5, 8.5 Hz, H_β), 7.99 (dd, 1H, J=1.3, 8.5 Hz, H_γ), 8.10 (dd, 1H, J=1.3, 4.5 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 53.3, 68.3, 71.2, 125.9, 130.3, 140.0, 146.8, 148.7; MS (CI) m/z 240 (M+1); Anal. calcd for $C_8H_9N_5O_4$: C, 40.17; H, 3.79; N, 29.28. Found: C, 40.33; H, 3.80; N, 29.36.

4.6. General procedure for the preparation of dioxinopyridines 8–12

To a solution or suspension of appropriate base (NaH, *t*-BuOK, LiH or KH, 3 mmol) in solvent (DME or *t*-BuOH, 5 mL) was added a solution of the appropriate alcohols **3**–**7** (1.5 mmol) in solvent (5 mL). The resulting mixture was heated (80 °C) for 4–72 h. After cooling to room temperature, the reaction was hydrolysed with H_2O and extracted with AcOEt. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a residue which was purified by column chromatography (eluent: MeOH/CH_2Cl_2, gradient: 0.2:9.8 to 1:9) to afford dioxinopyridines **8**–**12** (see Tables 1–4). Using as starting materials the chloro-derivatives **4b**, **6b** and **7b** (Table 3, entry 1, 5 and 9) only the isomers **9A**, **10A** and **11A** are obtained. The structure and the ratio of **9B**, **10B** and **11B** were deduced from the spectral data of their isomeric mixture.

4.6.1. 3-(4-Phenylpiperazin-1-ylmethyl)-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 8A. Mp 119–120 °C; IR (KBr) ν 1270 and 1240 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.64–2.87 (m, 6H, CH_2–N(CH_2)$_2$), 3.13–3.29 (m, 4H, Ph-N(CH_2)$_2$), 4.03 (dd, 1H, J=7.5, 11.5 Hz, O–CH_2–CH), 4.35 (dd, 1H, J=2.3, 11.5 Hz, O–CH_2–CH), 4.46–4.57 (m, 1H, O–CH$_2$–CH), 6.81–6.96 (m, 4H, H_β, H_{ar}), 7.18 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.21–7.31 (m, 2H, H_{ar}), 7.82 (dd, 1H, J=1.6, 4.8 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.3, 54.2, 58.4, 66.6, 72.7, 116.2, 118.5, 119.9, 124.7, 129.2, 139.1, 140.2, 150.9, 151.3; MS (CI) m/z 312 (M+1); Anal. calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.31; H, 6.75; N, 13.36.

4.6.2. 2-(4-Phenylpiperazin-1-ylmethyl)-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 8B. Oil; IR (film) ν 1277 and 1247 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60–2.82 (m, 6H, CH_2–N(CH_2)$_2$), 3.17–3.26 (m, 4H, Ph-N(CH_2)$_2$), 4.20 (dd, 1H, J=7.4, 11.4 Hz, O–CH_2–CH), 4.31–4.41 (m, 1H, O–CH$_2$–CH), 4.52 (dd, 1H, J=2.2, 11.4 Hz, O–CH_2–CH), 6.80–6.97 (m, 4H, H_β, H_{ar}), 7.20 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.25–7.31 (m, 2H, H_{ar}), 7.82 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 49.2, 54.0, 58.3, 67.5, 71.2, 116.2, 118.6, 119.9, 125.0, 129.2, 138.8, 140.0, 151.0, 151.3; MS (CI) m/z 312 (M+1); Anal. calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.39; H, 6.77; N, 13.56.

4.6.3. 3-Benzyloxymethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 9A. Mp 84–85 °C; IR (KBr) ν 1281 and 1240 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.71 (dd, 1H, J=6.4, 10.2 Hz, Ph-CH$_2$–O–CH_2), 3.83 (dd, 1H, J=4.5, 10.2 Hz, Ph-CH$_2$–O–CH_2), 4.09 (dd, 1H, J=7.5, 11.6 Hz, O–CH_2–CH), 4.33 (dd, 1H, J=2.3, 11.6 Hz, O–CH_2–CH), 4.45–4.55 (m, 1H, O–CH$_2$–CH), 4.59 (s, 2H, Ph-CH_2–O), 6.84 (dd, 1H, J=4.7, 7.8 Hz, H_β), 7.17 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.25–7.40 (m, 5H, H_{ar}), 7.81 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 65.4, 68.3, 73.0, 73.8, 118.5, 124.7, 127.8, 127.9, 128.5, 137.6, 139.0, 140.1, 150.8; MS (CI) m/z 258 (M+1); Anal. calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.17; H, 5.80; N, 5.56.

4.6.4. 2-Benzyloxymethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 9B. IR (film) ν 1281 and 1185 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.67 (dd, 1H, J=5.3, 10.4 Hz, Ph-CH$_2$–O–CH_2), 3.75 (dd, 1H, J=4.8, 10.4 Hz, Ph-CH$_2$–O–CH_2), 4.27 (dd, 1H, J=7.2, 11.0 Hz, O–CH_2–CH), 4.31–4.43 (m, 1H, O–CH$_2$–CH), 4.48 (dd, 1H, J=1.9, 11.0 Hz, O–CH_2–CH), 4.90 (s, 2H, Ph-CH_2–O), 6.86 (dd, 1H, J=4.7, 7.8 Hz, H_β), 7.20 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.28–7.45 (m, 5H, H_{ar}), 7.82 (dd, 1H, J=1.6, 4.7 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 66.3, 68.3, 72.1, 73.9, 118.7, 125.0, 127.9, 128.1, 128.7, 137.3, 138.9, 140.0, 150.9; MS (CI) m/z 258 (M+1); Anal. calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.23; H, 5.90; N, 5.60.

4.6.5. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl)-methylamine 10A. Oil; IR (film) ν 1190 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3); 2.70–2.80 (m, 2H, Ph-CH_2–N); 3.47 (d, 1H, J=13.1 Hz, Ph-CH$_2$–NH–CH_2); 3.60 (d, 1H, J=13.1 Hz, Ph-CH$_2$–NH–CH_2); 3.84 (dd, 1H, J=7.7, 11.5 Hz, O–CH_2–CH);

4.27 (dd, 1H, *J*=2.4, 11.5 Hz, O–C*H*$_2$–CH); 4.39–4.50 (m, 1H, O–CH$_2$–C*H*); 6.77 (dd, 1H, *J*=4.8, 7.9 Hz, H$_\beta$,); 7.10 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$); 7.21–7.29 (m, 5H, H$_{ar}$); 7.77 (dd, 1H, *J*=1.6, 4.8 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 43.4; 56.8; 62.9; 66.5; 72.6; 118.2; 124.4; 127.1; 128.2; 128.8; 138.6; 139.0; 139.8; 150.8; MS (CI) *m*/*z* 271 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.21; H, 6.80; N, 10.28.

4.6.6. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl)-methylamine 10B. IR (film) ν 1190 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.34 (s, 3H, CH$_3$); 2.60–2.68 (m, 2H, Ph-C*H*$_2$–N); 3.49 (d, 1H, *J*=13.1 Hz, Ph-CH$_2$–NH–C*H*$_2$); 3.60 (d, 1H, *J*=13.1 Hz, Ph-CH$_2$–NH–C*H*$_2$); 4.04 (dd, 1H, *J*=7.7, 11.5 Hz, O–*CH*$_2$–CH); 4.27 (dd, 1H, *J*=2.4, 11.5 Hz, O–C*H*$_2$–CH); 4.37–4.50 (m, 1H, O–CH$_2$–C*H*); 6.76 (dd, 1H, *J*=4.8, 7.9 Hz, H$_\beta$,); 7.11 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$); 7.22–7.30 (m, 5H, H$_{ar}$); 7.79 (dd, 1H, *J*=1.6, 4.8 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 43.5; 56.9; 63.1; 67.6; 71.5; 118.5; 124.8; 127.4; 128.4; 129.0; 138.5; 138.9; 139.8; 151.1; MS (CI) *m*/*z* 271 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.34; H, 6.62; N, 10.30.

4.6.7. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl)-amine 11A. Oil; IR (film) ν 1190 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.83 (broad s, 1H, NH), 2.94 (d, 2H, *J*=4.5 Hz, Ph-CH$_2$–NH–C*H*$_2$), 3.83 (s, 2H, Ph-C*H*$_2$–N), 4.05 (dd, 1H, *J*=8.1, 11.5 Hz, O–C*H*$_2$–CH), 4.26 (dd, 1H, *J*=2.3, 11.5 Hz, O–C*H*$_2$–CH), 4.40–4.51 (m, 1H, O–CH$_2$–C*H*), 6.84 (dd, 1H, *J*=4.9, 7.9 Hz, H$_\beta$), 7.16 (dd, 1H, *J*=1.7, 7.9 Hz, H$_\gamma$), 7.25–7.38 (m, 5H, H$_{ar}$), 7.80 (dd, 1H, *J*=1.7, 4.9 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 48.9, 54.0, 67.2, 72.7, 118.5, 124.9, 127.3, 128.2, 128.6, 138.9, 139.9, 140.0, 151.0; MS (CI) *m*/*z* 257 (M+1); Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.11; H, 6.30; N, 10.78.

4.6.8. Benzyl-(2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl)-amine 11B. IR (film) ν 1200 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.79 (broad s, 1H, NH), 2.97 (d, 2H, *J*=4.7 Hz, Ph-CH$_2$–NH–C*H*$_2$), 4.03 (s, 2H, Ph-C*H*$_2$–N), 4.13 (dd, 1H, *J*=7.9, 11.6 Hz, O–C*H*$_2$–CH), 4.41 (dd, 1H, *J*=2.3, 11.6 Hz, O–C*H*$_2$–CH), 4.45–4.56 (m, 1H, O–CH$_2$–C*H*), 6.87 (dd, 1H, *J*=4.8, 7.8 Hz, H$_\beta$), 7.20 (dd, 1H, *J*=1.7, 7.9 Hz, H$_\gamma$), 7.29–7.42 (m, 5H, H$_{ar}$), 7.81 (dd, 1H, *J*=1.6, 4.9 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 49.8, 54.0, 66.3, 72.8, 118.7, 125.2, 127.4, 128.4, 128.9, 138.6, 139.8, 139.9, 151.1; MS (CI) *m*/*z* 257 (M+1); Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.15; H, 6.37; N, 10.83.

4.6.9. 3-Azidomethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 12A. Oil; IR (film) ν 2108 (N$_3$), 1277 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.59 (d, 2H, *J*=5.6 Hz, CH–C*H*$_2$–N$_3$), 4.02 (dd, 1H, *J*=7.3, 11.6 Hz, O–C*H*$_2$–CH), 4.23 (dd, 1H, *J*=2.5, 11.6 Hz, O–C*H*$_2$–CH), 4.39–4.48 (m, 1H, O–CH$_2$–C*H*), 6.84 (dd, 1H, *J*=4.7, 7.8 Hz, H$_\beta$), 7.15 (dd, 1H, *J*=1.7, 7.8 Hz, H$_\gamma$), 7.79 (dd, 1H, *J*=1.7, 4.7 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 50.5, 65.0, 72.6, 118.8, 124.9, 138.7, 140.3, 150.2; MS (CI) *m*/*z* 193 (M+1); Anal. calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.12; H, 4.35; N, 29.08.

4.6.10. 2-Azidomethyl-2,3-dihydro[1,4]dioxino[2,3-*b*]pyridine 12B. Oil; IR (film) ν 2108 (N$_3$), 1277 (C–O–C) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.47 (d, 2H, *J*=5.3 Hz, CH–C*H*$_2$–N$_3$), 4.14 (dd, 1H, *J*=6.7, 11.1 Hz, O–C*H*$_2$–CH), 4.28–4.29 (m, 1H, O–CH$_2$–C*H*), 4.34 (dd, 1H, *J*=2.0, 11.1 Hz, O–C*H*$_2$–CH), 6.79 (dd, 1H, *J*=4.7, 7.8 Hz, H$_\beta$), 7.13 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$), 7.73 (dd, 1H, *J*=1.6, 4.7 Hz, H$_\alpha$); ^{13}C NMR (CDCl$_3$) δ 50.2, 65.6, 71.6, 118.7, 124.9, 138.0, 140.0, 150.2; MS (CI) *m*/*z* 193 (M+1); Anal. calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 50.08; H, 4.17; N, 29.20.

4.7. General procedure for the preparation of the compounds 13–15

A solution of dioxinopyridines **9**, **10** or **11** (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 **13**, **14** or **15** (82–88%).

(2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3 and 2-yl)-methanol (**13A**, **13B**), (2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3 and 2-ylmethyl)-methylamine (**14A**, **14B**), (2,3-dihydro[1,4]dioxino[2,3-*b*]pyridin-3 and 2-yl)-methylamine (**15A**, **15B**). The analytical data of **13A**, **13B**, **14A**, **14B**, **15A** and **15B** were in accordance with the values described in the literature 22.

4.8. Preparation of the compounds 17 from 13

p-Toluenesulfonyl chloride (2.85 g, 15.00 mmol) was added to a solution of alcohol **13A** (or **13B**) (10.00 mmol) in pyridine (20 mL) at 0 °C. The reaction mixture was stirred for 48 h then the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography (eluent: CH_2Cl_2) to give **16A** (87%) (or **16B**, 85%).

4.8.1. 2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl-4-methylbenzenesulfonate 16A. Oil; IR (film) ν 1350 and 1110 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.45 (s, 3H, CH$_3$), 4.07 (dd, 1H, *J*=6.7, 11.6 Hz, O–C*H*$_2$–CH), 4.17–4.40 (m, 3H, O–C*H*$_2$–CH, CH–C*H*$_2$–O–Ts), 4.51–4.65 (m, 1H, O–CH$_2$–C*H*), 6.87 (dd, 1H, *J*=5.0, 7.8 Hz, H$_\beta$), 7.18 (dd, 1H, *J*=1.6, 7.8 Hz, H$_\gamma$), 7.31–7.45 (m, 2H, H$_{ar}$), 7.72–7.93 (m, 3H, H$_\alpha$, H$_{ar}$); ^{13}C NMR (CDCl$_3$) δ 21.7, 64.2, 66.7, 71.3, 118.9, 125.1, 128.1, 130.1, 132.1, 138.6, 140.4, 145.5, 150.0; MS (CI) *m*/*z* 322 (M+1); Anal. calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36. Found: C, 56.15; H, 4.85; N, 4.28.

4.8.2. 2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl-4-methylbenzenesulfonate 16B. Oil; IR (film) ν 1345 and 1110 (SO$_2$) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.44 (s, 3H, CH$_3$), 4.14–4.29 (m, 3H, O–C*H*$_2$–C*H*), 4.37–4.47 (m, 2H, CH–C*H*$_2$–O–Ts), 6.86 (dd, 1H, *J*=4.9, 7.9 Hz, H$_\beta$), 7.10 (dd, 1H, *J*=1.7, 7.9 Hz, H$_\gamma$), 7.36 (d, 2H, *J*=8.1 Hz, H$_{ar}$), 7.75–7.84 (m, 3H, H$_\alpha$, H$_{ar}$); ^{13}C NMR (CDCl$_3$) δ 21.6, 64.8, 66.9, 70.1, 118.8, 125.0, 127.9, 130.0, 132.1, 137.9, 140.1, 145.4, 150.1; MS (CI) *m*/*z* 322 (M+1); Anal. calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36. Found: C, 56.19; H, 4.55; N, 4.29.

The compound **16A** (or **16B**) (0.38 mmol) was heated at 130 °C for 8 h in a sealed tube with a mixture of methylamine (2 M, 5 mL) and DMF (5 mL). Addition of H_2O, extraction by CH_2Cl_2, drying over $MgSO_4$ and removal of the solvent afforded a crude product, which purified by column chromatography (eluent: MeOH/CH_2Cl_2, 1:9), yielding 73% of the *N*-methylamine **14A** (or 63% of **14B**). The analytical data were identical with those reported above.

Under similar sulfonation reaction conditions described for **13**, the resulting amines **14A** and **14B** were converted into their sulfonated derivatives **17A** and **17B** in good yields 90 and 88%, respectively.

4.8.3. *N*-(2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-3-ylmethyl)-4,*N*-dimethylbenzenesulfonamide 17A. Mp 135–136 °C; IR (KBr) ν 1463 (CH_3), 1335 (SO_2), 1278 and 1163 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 3.33 (dd, 1H, J=4.8, 14.6 Hz, O–CH_2–CH), 3.42 (dd, 1H, J=5.6, 14.6 Hz, O–CH_2–CH), 4.15 (dd, 1H, J=7.3, 11.7 Hz, CH–CH_2–N–CH_3), 4.45 (dd, 1H, J=7.3, 11.7 Hz, CH–CH_2–N–CH_3), 4.50–4.61 (m, 1H, O–CH_2–C*H*), 6.88 (dd, 1H, J=4.6, 7.8 Hz, H_β), 7.22 (dd, 1H, J=1.6, 7.8 Hz, H_γ), 7.35 (d, 2H, J=8.2 Hz, H_{ar}), 7.69 (d, 2H, J=8.2 Hz, H_{ar}), 7.82 (dd, 1H, J=1.5, 4.6 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 21.7, 37.6, 50.5, 65.7, 73.3, 118.8, 125.0, 127.5, 130.0, 134.0, 139.0, 140.2, 144.0, 150.5; MS (CI) *m/z* 335 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.35; H, 5.39; N, 8.28.

4.8.4. *N*-(2,3-Dihydro[1,4]dioxino[2,3-*b*]pyridin-2-ylmethyl)-4,*N*-dimethylbenzenesulfonamide 17B. Mp 99–100 °C; IR (KBr) ν 1474 (CH_3), 1397 (SO_2), 1285 and 1153 (C–O–C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.26 (d, 2H, J=5.6 Hz, CH–CH_2–N–CH_3), 4.23 (dd, 1H, J=6.9, 11.6 Hz, O–CH_2–CH), 4.32–4.44 (m, 1H, O–CH_2–C*H*), 4.50 (dd, 1H, J=2.2, 11.6 Hz, O–CH_2–CH), 6.83 (dd, 1H, J=4.7, 7.9 Hz, H_β), 7.11 (dd, 1H, J=1.6, 7.9 Hz, H_γ), 7.25–7.35 (m, 2H, H_{ar}), 7.60–7.70 (m, 2H, H_{ar}), 7.78 (dd, 1H, J=1.6, 4.67 Hz, H_α); ^{13}C NMR ($CDCl_3$) δ 21.5, 37.4, 50.2, 66.4, 72.0, 118.7, 125.0, 127.4, 129.9, 134.0, 138.3, 140.1, 143.9, 150.6; MS (CI) *m/z* 335 (M+1); Anal. calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38. Found: C, 57.38; H, 5.34; N, 8.47.

4.9. Preparation of the amines 15 from 12

Azide **12A** (or **12B**) (2.6 mmol) in EtOH (16 mL) was stirred with Lindlar palladium (0.08 mmol) in Parr apparatus under hydrogen pressure (30 psi). After 4 h, palladium was filtered and washed with EtOH. The solvent was evaporated and a column chromatography (eluent: MeOH/CH_2Cl_2, 1:9) afforded the product **15A** as an oil in 99% yield (**15B** in 95% yield). The analytical data were identical with those reported above.

4.10. Preparation of the compounds 8 from 15

N,N-Bis(2-chloroethyl)aniline (1.0 g, 4.60 mmol), sodium hydrogen carbonate (1.16 g, 13.80 mmol), sodium iodide (1.38 g, 9.20 mmol) were added to a solution of the amine **15A** or **15B** (9.20 mmol) in ethylene glycol (40 mL). The reaction mixture was stirred at 110 °C for 1.5 h. The solution was cooled 25 °C and concentrated under reduced pressure. The residue was taken in CH_2Cl_2 and washed with H_2O. The organic layer was dried ($MgSO_4$) and the solvent was removed. The residue was subjected to flash silica gel chromatography (eluent: MeOH/CH_2Cl_2, 1:9) to afford the product **8A** in 69% yield (**8B** in 65% yield). The analytical data were identical with those reported above.

Acknowledgements

The authors thank Dr. J. Willems from Janssen Pharmaceutica for his significant remark concerning our article cited in the Ref. 22.

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Table 1. Conditions of cyclization reactions of alcohols **2**–**5**

Entry	Y	Base/solvent	*T* (°C)/*t* (h)	Yield %	Ratio **A/B**
5	CH_2NHCH_2Ph	NaH/DME	80/12	90	45/55
		t-BuOK/*t*-BuOH	80/12	89	30/70

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