A NEW SYNTHETIC ROUTE TO THE PREVIOUSLY UNATTAINABLE 3-SUBSTITUTED 2,3-DIHYDRO-1,4-DIOXINO[2,3-*b*]PYRIDINES

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Abstract -A variety of 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines (**3**) have been synthesized from the readily available 2-chloro-3-oxiranylmethoxypyridine (**1**). Treatment of this epoxide by various nucleophile reagents provided alcohols (**2a-i**) which, by displacement of the chlorine, gave the desired products (**3a-i**) in satisfactory yields.

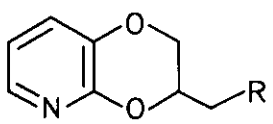
Ever since Fourneau and Bovet[1] first described 2,3-dihydro-1,4-benzodioxins as epinephrine antagonists, a large number of related compounds possessing similar properties have been reported. Examples include piperoxan,[2] prosympal,[3] dibozane,[4] and structures incorporating both the 2,3-dihydro-1,4-benzodioxin and alkylamine moiety (MDL 72832[5]), aryloxyalkylamine moiety (WB 4101[6]) or arylpiperazine moiety (flesinoxan,[7] eltoprazine[8]). Some of these compounds often have a complex pharmacological profile such as WB 4101, known for both its 5-HT and α-blocking properties.[9] Paradoxically, despite the considerable development of procedures to efficiently construct the nitrogen-containing ring, the 1,4-dioxino-[2,3-*b*]pyridine skeleton has still remaind inaccessible.

To our knowledge the only reported methods for the elaboration of this polyheterocyclic system consists in the treatment of 3-hydroxy-2-pyridone with either sodium hydride and 1,2-dibromoethane in hexamethylphosphorous triamide,[10] potassium carbonate and 1,2-dibromoethane in dimethylformamide,[11] or potassium carbonate and 1,2-dibromoethane in dimethylacetamide.[12] These methods, unfortunately too restrictive, not only give unsatisfactory reaction yields but also make the introduction of various substituents in the six-membered non aromatic moiety infeasible.

In connection with our studies on polycondensed heterocycles with potential biological activity,[13-15] we now

report a general, novel and effective synthetic approch to the previously unattainable 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines (**3**).

Figure 1



3

Our strategy consists in reacting epoxide (**1**) with various nucleophiles to give alcohols (**2a-i**) by way of the oxirane ring opening. Intramolecular ring closure afforded the desired 3-alkyldioxinopyridines (**3a-i**) in satisfactory yields (Scheme I).

Epoxide (**1**) was prepared by treatment of 2-chloro-3-pyridinol with excess epichlorohydrin using sodium hydride in DMF. These conditions led to the efficient conversion to the epoxide which was used after purification for reactions with nucleophiles.

The ring opening of epoxide (**1**) with amines was promoted by use of THF at reflux to afford the corresponding amino alcohols in excellent yields. When a volatile amine was used (isopropylamine), the reaction was done with a great excess of the amine. For the cases of the high boiling piperidine and phenylpiperazine, the reaction was carried out with only 3 molar equiv. The resulting amino alcohols (**2a-c**) were not purified, but used directly for the subsequent cyclization reaction.

Methanolysis of epoxide (**1**) at 0 °C in the presence of a catalytic amount of boron trifluoride ether complex[16] afforded the 3-methoxy-1-(2-chloro-3-pyridinyloxy)-2-propanol (**2d**) (76%).

To synthesize the aryl alkyl ether (**2e**), we found that a stirring slurry of activated commercially available Woelm 200 neutral chromatographic alumina (500 °C, 24 h) catalyzed the opening of epoxide (**1**) by 10 molar equiv. of benzyl alcohol under mild conditions (25 °C, THF).[17] Alumina "doped" with this nucleophile opened the epoxide (**1**) regioselectively and gave the corresponding functionalized alcohol (**2f**) in good yields (83%).

The ring opening of epoxide (**1**) with trimethylsilyl phenoxide[18] was promoted by use of 4 mol % of cesium fluoride as a catalyst[19] in a closed system at 130 °C for 1 h to give the corresponding trimethylsilyl ether (76%). Deblocking of the silyl group furnished the alcohol (**2f**) in nearly quantitative yields.

Reduction of epoxide (**1**) with lithium aluminum hydride in THF at room temperature,[20] led to the attack of the hydride at the least substituted carbon to form the product (**2g**) (88%).

For the synthesis of the azido alcohol (**2h**), epoxide (**1**) was opened regioselectively with sodium azide in aqueous dioxane[21] (88%).

Lipshutz and co-workers[22] reported that the reaction of mixed cuprates $R_2Cu(CN)Li_2$ formed from copper cyanide and 2 equiv. of organolithium with oxiranes gave an alkylated product ethanol derivative in good yields. Moreover, Alexakis[23] showed that nucleophilic opening of poorly reactive epoxides by organocopper and cuprate reagents was dramatically enhanced in the presence of BF_3. Thus, treatment of epoxide (**1**) with 1.5 molar equiv. of $Me_2Cu(CN)Li_2$ in the presence of an ether-boron trifluoride complex at -78 °C for 30 min furnished the corresponding alcohol (**2i**) in 92% yield.

After experimenting with a variety of conditions and methods, it was found that the best result for the intramolecular cyclization was obtained using a sodium hydride in a 1,2-dimethoxyethane solvent at reflux (Scheme I). 3-Substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines (**3a-i**) were then obtained in moderate yields (54-63%).

This study represents the first convenient and effective synthetic route to the barely accessible 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines. The starting material for this novel approach is readily available, and suitable for preparing derivatives having a wide variety of substituents.

Scheme I

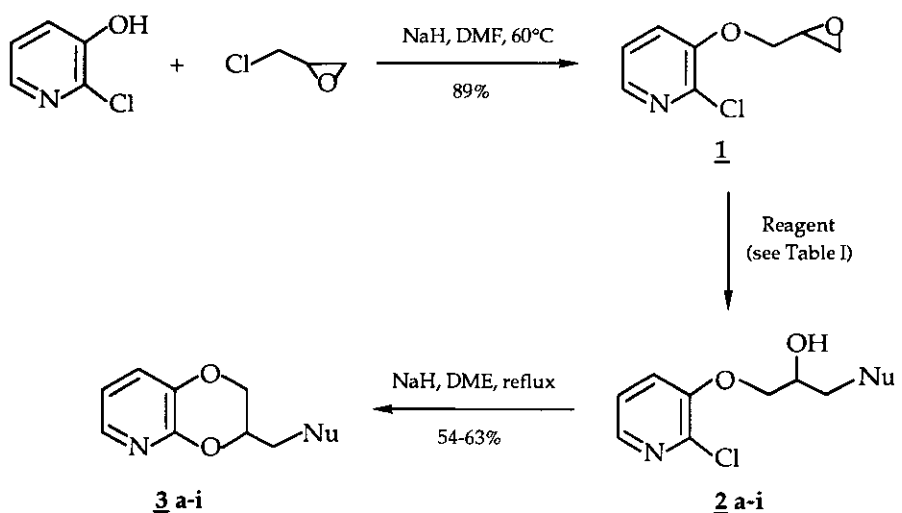
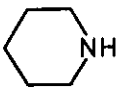
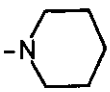
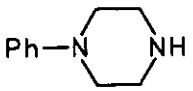
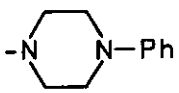


Table I. Reaction of epoxide 1 with various nucleophiles

Reagent	Experimental Conditions	Product	-Nu	Yield %
$(CH_3)_2CHNH_2$	THF, reflux, 24 h	**2a**	$-NHCH(CH_3)_2$	94[a]
	THF, reflux, 24 h	**2b**		94[a]
	THF, reflux, 24 h	**2c**		100[a]
CH_3OH	CH_3OH, $BF_3.Et_2O$, 0 °C	**2d**	$-OCH_3$	76[b]
$PhCH_2OH$	THF, Al_2O_3, room temperature, 24 h	**2e**	$-OCH_2Ph$	83[b]
$PhOSi(CH_3)_3$	CsF, 130 °C, 1 h[c]	**2f**	-OPh	76[b,d]
$LiAlH_4$	THF, room temperature, 30 min	**2g**	-H	88[b]
NaN_3	Dioxane/H_2O, reflux, 7 h	**2h**	$-N_3$	88[b]
$(CH_3)_2Cu(CN)Li_2$	THF, -78 °C, 30 min	**2i**	$-CH_3$	92[b]

[a] Yield of crude product based on epoxide (1) ; [b] Yields of isolated products based on epoxide (1) after flash chromatography, not optimized ; [c] The reaction was run without solvent ; [d] Yield of alcohol (**2f**) based on epoxide (1) after the desilylation step.

EXPERIMENTAL

Melting points are uncorrected. ^1H Nmr (300 MHz) spectra were run on a Bruker AM 300 WB spectrometer. TMS served as internal standard. Ir spectra of liquid films or KBr pellets were recorded on a Perkin-Elmer 297 instrument. Mass spectra were registered on a Nermag R-10-10-C apparatus. Reaction products were purified by flash column chromatography using silica gel (Merck 230-400 mesh) according to Still.[24] Analytical tlc were performed on silica gel F_{254} plates. All air- and moisture-sensitive reactions were conducted under a prepurified argon atmosphere in flame-dried glassware. Anhydrous solvents were transferred via syringe.

2-Chloro-3-oxiranylmethoxypyridine (1). To NaH (1.58 g of a 50% oil dispersion, 33 mmol) in DMF (30 ml) was added dropwise a solution of 2-chloro-3-pyridinol (3.88, 30 mmol) in DMF (30 ml) for 1 h. After

stirring for 30 min, a solution of epichlorohydrin (27.7 g, 300 mmol) in DMF (30ml) was added. After stirring 3 days at 60 °C, the mixture was filtered and the DMF was removed under reduced pressure. H_2O (60 ml) was added to the residue and the oil was extracted with CH_2Cl_2 (3x30 ml). After drying ($MgSO_4$) and concentration, the residue was purified by flash chromatography (8:2 to 3:7 , petroleum ether/Et_2O) to give 5 g (89%) of **1** as a yellow oil which slowly crystallized on standing: mp 35-36 °C; ir (KBr) 1280 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 2.81 (dd, *J* = 2.7 and 4.6 Hz, 1H), 2.92 (t, *J* = 4.6 Hz, 1H), 3.40-3.46 (m, 1H), 4.04 (dd, *J* = 5.4 and 11.4 Hz, 1H), 4.36 (dd, *J* = 2.8 and 11.4 Hz, 1H), 7.18 (dd, *J* = 4.7 and 8.0 Hz, 1H), 7.27 (dd, *J* = 1.2 and 8.0 Hz, 1H), 8.01 (dd, *J* = 1.2 and 4.7 Hz, 1H). *Anal.* Calcd for $C_8H_8NO_2Cl$: C, 51.76; H, 4.34; N, 7.54. Found: C, 51.59; H, 4.31; N, 7.46.

1-(2-Chloro-3-pyridinyloxy)-3-methylethylamino-2-propanol (2a). To a solution of **1** (1.25 g, 6.73 mmol) in dry THF (30 ml) was added isopropylamine (9.95 g, 168 mmol). The mixture was stirred at reflux for 24 h then diluted with water (50 ml), extracted with CH_2Cl_2 (3x25 ml), dried ($MgSO_4$) and concentrated to give 1.55 g (94%) of **2a** as a white solid: mp 99-100 °C; ir (KBr) 3400-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 1.10 (d, *J* = 6.3 Hz, 6), 2.79-3.00 (m, 3H), 4.00-4.14 (m, 3H), 7.19 (dd, *J* = 4.7 and 8.5 Hz, 1H), 7.25 (dd, *J* = 1.4 and 8.5 Hz, 1H), 8.00 (dd, *J* = 1.4 and 4.7 Hz, 1H). *Anal.* Calcd for $C_{11}H_{17}N_2O_2Cl$: C, 53.98; H, 7.00; N, 11.45. Found: C, 54.12; H, 7.08; N, 11.48.

1-(2-Chloro-3-pyridinyloxy)-3-(1-piperidinyl)-2-propanol (2b). Following the procedure described for **2a** but substituting isopropylamine by piperidine (1.7 g, 20 mmol), 1.79 g of **2b** (98%) was obtained as a white solid: mp 97-98 °C; ir (KBr) 3000-3500 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 1.40-1.66 (m, 6H), 2.34-2.68 (m, 6H), 4.04-4.20 (m, 3H), 7.19 (dd, *J* = 4.7 and 8.5 Hz, 1H), 7.28 (dd, *J* = 1.4 and 8.5 Hz, 1H), 8.01 (dd, *J* = 1.4 and 4.7 Hz, 1H). *Anal.* Calcd for $C_{13}H_{19}N_2O_2Cl$: C, 57.66; H, 7.07; N, 10.35. Found: C, 57.74; H, 7.21; N, 10.27.

1-(2-Chloro-3-pyridinyloxy)-3-(4-phenyl-1-piperazinyl)-2-propanol (2c). Following the procedure described for **2a** but substituting isopropylamine by 3.28 g (20 mmol) of 1-phenylpiperazine, purification of the residue by flash chromatography (Et_2O) yielded 2.30 g (98%) of **2c** as a white solid: mp 107-108 °C; ir (KBr) 3500-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 2.60-2.89 (m, 6H), 3.15-3.31 (m, 4H), 4.06-4.14 (m, 2H), 4.15-4.24 (m, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.93 (d, J = 8.1 Hz, 2H), 7.19 (dd, *J* = 4.7 and 8.3 Hz, 1H), 7.23-7.31 (m, 3H), 8.01 (dd, *J* = 1.3 and 4.7 Hz, 1H). *Anal.* Calcd for $C_{18}H_{22}N_3O_2Cl$: C, 62.15; H, 6.37; N, 12.08. Found: C, 62.28; H, 6.43; N, 12.19.

1-(2-Chloro-3-pyridinyloxy)-3-methoxy-2-propanol (2d). To a solution of **1** (500, 2.69 mmol) in methanol (6 ml) was added $Et_2O.BF_3$ (9.92 ml, 3% mol) at 0 °C with stirring, and stirring was continued for 8 h at room temperature. After evaporation of the solvant *in vacuo*, the residue was purified by flash chromatography (Et_2O) to give 442 mg (76%) of **2d** as a yellow oil: Ir (neat) 3500-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 3.42 (s, 3H), 3.60 (d, *J* = 5.0 Hz, 2H), 4.08 (dd, *J* = 5.8 and 9.9 Hz, 1H), 4.12 (dd, *J* = 4.1 and 9.9 Hz, 1H), 4.16-4.29 (m, 1H), 7.18 (dd, *J* = 4.7 and 7.9 Hz, 1H), 7.33 (dd, *J* = 7.9 and 1.6 Hz, 1H), 8.02 (dd, *J* = 1.6 and 4.7 Hz, 1H). *Anal.* Calcd for $C_9H_{12}NO_3Cl$: C, 49.66; H, 5.56; N, 6.43. Found: C, 49.51; H, 5.49; N, 6.38.

1-(2-Chloro-3-pyridinyloxy)-3-phenylmethoxy-2-propanol (2e). Epoxide(**1**)(1 g, 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 (5.82 g, 53.8 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 methanol. The combined washings were concentrated, and the residue was purified by flash chromatography (2:1 , Et_2O/petroleum ether) to leave 1.32 g (83 %) of **2e** as a yellow oil: Ir (neat) 3500-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 3.72 (d, *J* = 5.1 Hz, 2H), 4.12 (dd, *J* = 5.9 and 9.2 Hz, 1H), 4.14 (dd, *J* = 4.7 and 9.2 Hz, 1H), 4.19-4.27 (m, 1H), 4.59 (s, 2H), 7.16-7.35 (m, 7H), 8.2 (dd, *J* = 1.6 and 4.5 Hz, 1H). *Anal.* Calcd for $C_{15}H_{16}NO_3Cl$: C, 61.33; H, 5.49; N, 4.77. Found: C, 61.22; H, 5.41; N, 4.69.

1-(2-Chloro-3-pyridinyloxy)-3-phenoxy-2-propanol (2f). A mixture of **1** (300 mg, 1.61 mmol) and trimethylsilylphenoxide [18] (322 mg, 1.93 mmol) in the presence of cesium fluoride (10 mg, 4 mol %) was heated at 130 °C for 1 h in a closed system. Flash chromatography (Et_2O) afforded 432 mg (76%) of 1-(2-chloro-3-pyridinyloxy)-3-phenoxy-2-trimethylsilyloxypropane as a yellow oil. The trimethylsilyl ether of **2f** (284 mg, 0.8 mmol) was dissolved in THF (4 ml) containing a solution of aqueous HCl 2N (2 ml). The mixture was stirred at room temperature (2 h) and saponified with 4 ml of aqueous 2 N potassium hydroxide, extracted with CH_2Cl_2 (2x10 ml), dried ($MgSO_4$) and concentrated. Flash chromatography (Et_2O) gave 222 mg (98%) as an oil: Ir (neat) 3500-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 4.19-4.29 (m, 4H), 4.40-4.51 (m, 1H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.98 (t, *J* = 7.9 Hz, 1H), 7.20 (dd, *J* = 4.7 and 7.9 Hz, 1H), 7.27 (dd, *J* = 1.6 and 7.9 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 8.03 (dd, *J* = 1.6 and 4.7 Hz, 1H). *Anal.* Calcd for $C_{14}H_{14}NO_3Cl$: C, 60.11; H, 5.05; N, 5.00. Found: C, 60.23; H, 5.15; N, 5.09.

1-(2-Chloro-3-pyridinyloxy)-2-propanol (2g). A solution of **1** (695 mg, 3.74 mmol) in dry THF (8 ml) was

added dropwise over 10 min to an ice-cold suspension of lithium aluminum hydride (142 mg, 3.74 mmol) in THF (4 ml). After the addition was complete, the mixture was stirred at room temperature for 30 min. Excess reducting agent was decomposed with water (10 ml), and the inorganic solid salts were filtered off and washed with THF. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (Et_2O) to afford 619 mg (88%) of **2g** as an oil: Ir (neat) 3500-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 1.33 (d, *J* = 6.2 Hz, 3H), 3.89 (dd, *J* = 6.9 and 9.7 Hz, 1H), 4.02 (dd, *J* = 2.8 and 9.7, 1H), 4.22-4.30 (m, 1H), 7.19 (dd, *J* = 4.7 and 8.0 Hz, 1H), 7.23 ;(dd, *J* = 1.9 and 8.0 Hz, 1H), 7.99 (dd, *J* = 1.9 and 4.7 Hz, 1H). *Anal.* Calcd for $C_8H_{10}NO_2Cl$: C, 51.21; H, 5.37; N, 7.46. Found: C, 51.32; H, 5.49; N, 7.39.

1-(2-Chloro-3-pyridinyloxy)-3-azido-2-propanol (2h). Epoxide (**1**) (1.07g, 5.77 mmol) was dissolved in dioxane (23 ml) and treated with NaN_3 (525 mg, 8 mmol) in H_2O (6 ml). The mixture was heated at reflux for 7 h, cooled and the solvent removed *in vacuo*. The residue was partitioned between water and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 (3x25 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give crude **2h**. This was purified by flash chromatography (3:1 , Et_2O/petroleum ether) to afford 1.16 g (88%) of **2h** as an oil: Ir (neat) 3400-3200, 2095 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 3.56 (dd, *J* = 6.0 and 12.9 Hz, 1H), 3.61 (dd, *J* = 3.5 and 12.9 Hz, 1H), 4.10 (d, *J* = 5.1 Hz, 2H), 4.20-4.28 (m, 1H), 7.19-7.40 (m, 2H), 8.04 (dd, *J* = 1.9 and 4.3 Hz, 1H). *Anal.* Calcd for $C_8H_9N_4O_2Cl$: C, 42.02; H, 3.96; N, 24.50. Found: C, 42.15; H, 4.02; N, 24.67.

1-(2-Chloro-3-pyridinyloxy)-2-butanol (2i). To a stirred mixture of CuCN (193 mg, 2.15 mmol) and dry THF (2 ml) was added methyllithium (2.69 ml of 1.6 *M* solution in ether, 4.3 mmol) dropwise at 0 °C. The mixture was then cooled to -78 °C, and $BF_3.Et_2O$ (0.14 ml, 1.14 mmol) was added followed by addition of **1** (200 mg, 1.07 mmol) in dry THF (3 ml). The reaction mixture was allowed to warm slowly to room temperature and was quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2 (3x10 ml) and dried ($MgSO_4$). The crude product was purified by flash chromatography (2:1 , Et_2O/petroleum ether) to afford 199 mg (92%) of **2i** as an oil: Ir (neat) 3500-3200 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$ + D_2O) δ: 1.07 (t, *J* = 7.1 Hz, 3H), 1.66 (m, 2H), 3.92 (dd, *J* = 7.1 and 8.7 Hz, 1H), 3.99-4.04 (m, 1H), 4.06 (dd, *J* = 3.2 and 8.7 Hz, 1H), 7.19 (dd, *J* = 4.1 and 8.3 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 4.1 Hz, 1H). *Anal.* Calcd for $C_9H_{12}NO_2Cl$: C, 53.60; H, 6.00; N, 6.94. Found: C, 53.76; H, 6.09; N, 7.02.

Preparation of 3-substituted-2,3-dihydro-1,4-dioxino[2,3-*b*]pyridines (3a-i); General Procedure. The alcohols **(2a-i)** (1.5 mmol) dissolved in anhydrous DME (5 ml) were added to a magnetically stirred

suspension of NaH (79 mg of 50% oil dispersion, 1.65 mmol) in DME (5 ml) under nitrogen. After stirring 24 h at 82 °C, the mixture was filtered and the DME was removed under reduced pressure. H_2O was added to the residue, and the oil was extracted with CH_2Cl_2 (3x15 ml). After drying ($MgSO_4$) and concentration, purification and identification of the compounds (**3a-i**) were performed as indicated below. In all cases compounds (**3a-i**) separated out as oils except for compounds (**3c**), (**3f**) and (**3h**).

2,3-Dihydro-*N*-(1-methylethyl)-1,4-dioxino[2,3-*b*]pyridine-3-methanamine (**3a**). This compound obtained in 60% yield, was purified by flash chromatography (95:5 , CH_2Cl_2/MeOH): Ir (neat) 1270,1240 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.02 (s, 3H), 1.03 (s, 3H), 2.01 (s, 1H), 2.76-2.88 (m, 1H), 2.91 (d, J = 5.2 Hz, 2H), 4.09 (dd, *J* = 8.1 and 11.0 Hz, 1H), 4.27 (dd, *J* = 2.2 and 11.0 Hz, 1H), 4.38-4.47 (m, 1H), 6.81 (dd, *J* = 5.1 and 8.1 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 5.1 Hz, 1H); ms *m/z*: 209 (M^+ + 1). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.43; H, 7.74; N, 13.45. Found: C, 63.51; H, 7.82; N, 13.51.

1-[((2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridine)-3-yl)methyl]piperidine (**3b**). This compound obtained in 63% yield, was purified by flash chromatography (Et_2O): Ir (neat) 1285,1205 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.37-1.78 (m, 6H), 2.37-2.75 (m, 6H), 3.97 (dd, *J* = 7.8 and 11.9 Hz, 1H), 4.34 (dd, *J* = 2.5 and 11.9 Hz, 1H), 4.41-4.50 (m, 1H), 6.83 (dd, *J* = 4.7 and 7.6 Hz, 1H), 7.16 (dd, *J* = 1.4 and 7.6 Hz, 1H), 7.80 (dd, *J* = 1.4 and 4.7 Hz, 1H); ms *m/z*: 235 (M^+ + 1). *Anal.* Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.95. Found: C, 66.78; H, 7.79; N, 11.87.

1-[((2,3-Dihydro-1,4-dioxino[2,3-*b*]pyridine)-3-yl)methyl]-4-phenylpiperazine (**3c**). This compound obtained in 61% yield, was purified by flash chromatography (Et_2O): mp 119-120 °C; ir (KBr) 1270, 1240 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 2.66-2.86 (m 6H), 3.12-3.26 (m, 4H), 4.04 (dd, *J* = 7.6 and 11.7 Hz, 1H), 4.40 (dd, *J* = 2.2 and 11.7 Hz, 1H), 4.46-4.56 (m, 1H), 6.85 (t, *J* = 7.7 Hz, 1H), 6.89 (dd, *J* = 4.6 and 7.7 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 2H), 7.18 (dd, *J* = 1.1 and 7.7 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.82 (dd, *J* = 1.1 and 4.6, 1H); ms *m/z*: 312 (M^+ + 1). *Anal.* Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.79; N, 13.49. Found: C, 69.57; H, 6.85; N, 13.39.

2,3-Dihydro-3-[(methoxy)methyl]-1,4-dioxino[2,3-*b*]pyridine (**3d**). This compound obtained in 54% yield, was purified by flash chromatography (1:2 , Et_2O/petroleum ether): Ir (neat) 1285 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 4.45 (s, 3H), 3.63 (dd, *J* = 6.2 and 10.4 Hz, 1H), 3.75 (dd, *J* = 4.1 and 10.4 Hz, 1H), 4.05 (dd, *J* = 6.9 and 11.7 Hz, 1H), 4.32 (dd, *J* = 2.1 and 11.7 Hz, 1H), 4.44-4.52 (m, 1H), 6.85 (dd, *J* = 4.7 and 7.6 Hz, 1H), 7.16 (dd, *J* = 1.2 and 7.6 Hz, 1H), 7.81 (dd, *J* = 1.2 and 4.7 Hz, 1H); ms *m/z*: 182 (M^+ + 1). *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.73; H, 6.19; N, 7.66.

2,3-Dihydro-3-[(phenylmethoxy)methyl]-1,4-dioxino[2,3-*b*]pyridine (3e). This compound obtained in 62% yield, was purified by flash chromatography (1:2 , Et_2O/petroleum ether): Ir (neat) 1190 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 3.71 (dd, *J* = 6.7 and 10.0 Hz, 1H), 3.83 (dd, *J* = 4.6 and 10.0 Hz, 1H), 4.07 (dd, *J* = 7.2 and 11.8 Hz, 1H), 4.40 (dd, *J* = 2.0 and 11.8 Hz, 1H), 4.45-4.57 (m, 1H), 4.61 (s, 2H), 6.83 (dd, *J* = 4.7 and 7.6 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.24-7.39 (m, 5H), 7.80 (d, *J* = 4.7 Hz, 1H); ms *m/z*: 258 (M^+ + 1). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 70.14; H, 5.93; N, 5.56.

2,3-Dihydro-3-[(phenoxy)methyl]-1,4-dioxino[2,3-*b*]pyridine (3f). This compound obtained in 63% yield, was purified by flash chromatography (1:1 , Et_2O/petroleum ether): mp 83-84 °C; ir (KBr) 1270,1240 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 4.13-4.24 (m, 2H), 4.34 (dd, *J* = 3.9 and 11.1 Hz, 1H), 4.44 (dd, *J* = 2.0 and 11.1 Hz, 1H), 4.67-4.76 (m, 1H), 6.88 (dd, *J* = 4.7 and 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 4.7 Hz, 1H); ms *m/z*: 244 (M^+ + 1). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.38; N, 5.76. Found: C, 69.19; H, 5.48; N, 5.65.

2,3-Dihydro-3-methyl-1,4-dioxino[2,3-*b*]pyridine (3g). This compound obtained in 61% yield, was purified by flash chromatography (2:1 , Et_2O/petroleum ether): Ir (neat) 1290 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.42 (d, *J* = 6.4 Hz, 3H), 3.82 (dd, *J* = 8.2 and 11.4 Hz, 1H), 4.20 (dd, *J* = 2.5 and 11.4 Hz, 1H), 4.39-4.49 (m, 1H), 6.83 (dd, *J* = 4.6 and 7.7 Hz, 1H), 7.16 (dd, *J* = 1.0 and 7.7 Hz, 1H), 7.80 (dd, *J* = 1.0 and 4.6 Hz, 1H); ms *m/z*: 152 (M^+ + 1). *Anal.* Calcd for $C_8H_9NO_2$: C, 79.30; H, 7.48; N, 11.56. Found: C, 79.45; H, 7.59; N, 11.48.

2,3-Dihydro-3-azidomethyl-1,4-dioxino[2,3-*b*]pyridine (3h). This compound obtained in 62% yield, was purified by flash chromatography (1:1 , Et_2O/petroleum ether): mp 63-64 °C; ir (neat) 2110, 1180, 1190 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 3.61 (dd, *J* = 5.8 and 12.6 Hz, 1H), 3.66 (dd, *J* = 5.2 and 12.6 Hz, 1H), 4.06 (dd, *J* = 7.2 and 11.2 Hz, 1H), 4.27 (dd, *J* = 2.8 and 11.6 Hz, 1H), 4.43-4.51 (m, 1H), 6.88 (dd, *J* = 4.7 and 7.9 Hz, 1H), 7.19 (dd, *J* = 1.4 and 7.9 Hz, 1H), 7.76 (dd, *J* = 1.4 and 4.7 Hz, 1H); ms *m/z*: 193 (M^+ + 1). *Anal.* Calcd for $C_8H_8N_4O_2$: C, 50.00; H, 4.19; N, 29.15. Found: C, 50.14; H, 4.22; N, 29.27.

2,3-Dihydro-3-ethyl-1,4-dioxino[2,3-*b*]pyridine (3i). This compound obtained in 62% yield, was purified by flash chromatography (2:1 , Et_2O/petroleum ether): Ir (neat) 1260, 1235 cm^{-1} ; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.09 (t, *J* = 7.1 Hz, 3H), 1.59-1.84 (m, 2H), 3.83 (dd, J = 8.5 and 11.8 Hz, 1H), 4.19 (dd, J = 2.4 and 11.8 Hz, 1H), 4.14-4.23 (m, 1H), 6.79 (dd, J = 4.7 and 7.9 Hz, 1H), 7.13 (dd, J = 1.2 and 7.9 Hz, 1H), 7.78 (dd, J = 1.2 and 4.7 Hz, 1H); ms *m/z*: 166 (M^+ + 1). *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.59; H, 6.81; N, 8.41.

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