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SYNTHESIS OF SUBSTITUTED OXAZOLO[4,5-*b*]-PYRIDINE DERIVATIVES

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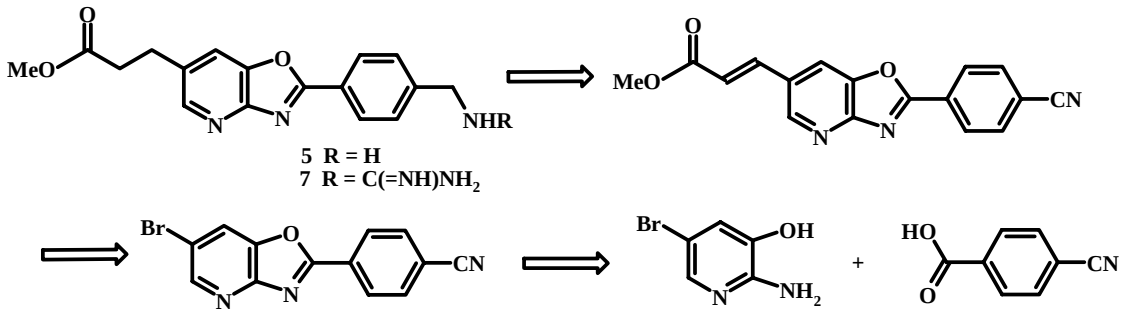
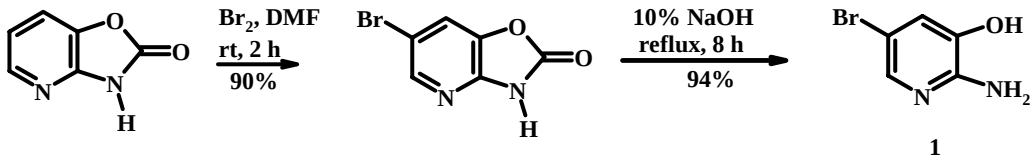
Abstract- Synthesis of new functionnalized oxazolo[4,5-*b*]pyridines was described. 5-Bromo-3-hydroxy-2-aminopyridine was heated, in the presence of PPSE or PPA, with 4-cyanobenzoic acid, (4-piperidinyl)acetic or propanoic acid to afford 1,3-oxazolo derivatives. Introduction of a carboxylic acid moiety on the pyridine framework was carried out using Heck reaction. The basic moiety, also required for GPIIb/GPIIIa antagonism, was generated by guanylation.

In the search of new non-peptidic glycoprotein GPIIb/GPIIIa antagonists[1,2] we have explored heterocyclic scaffolds such as 1,4-benzoxazine or indole. In this paper we reported our results in the use of oxazolo[4,5-*b*]pyridine as framework, having an acidic and a basic chains which may confer the pharmacological properties to the desired molecules. Oxazolo[4,5-*b*]pyridines were usually obtained by action of acid chloride[3] or dithioketal[4] on 2-amino-3-hydroxypyridine in a basic medium. Polyphosphoric acid (PPA) or *p*-toluenesulfonic acid (PTSA) have been also used with aromatic carboxylic acid[5-7] or aliphatic acid[8] to generate the oxazolo ring. For our own part, we have developped in our group[9] a milder synthesis using polyphosphoric acid trimethylsilyl ester (PPSE)[10] instead of PPA. We planned to prepare compounds (**5**) and (**7**) according to Scheme 1.



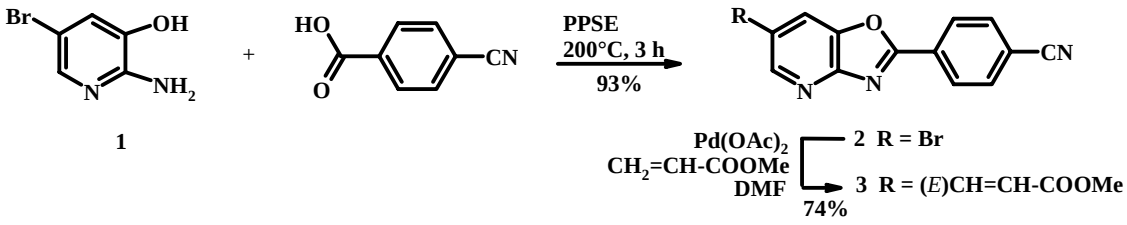
Scheme 1

The starting material, 2-amino-5-bromo-3-hydroxypyridine (**1**) was not obtained by direct bromination of 2-amino-3-hydroxypyridine. In fact, oxazolo[4,5-*b*]pyridine-2(3*H*)-one[11] which was a masked form of 2-amino-3-hydroxypyridine was brominated according to our method[12] (yield 90%); the oxazolone ring was then hydrolyzed in basic medium to give compound (**1**) in 94 % yield (Scheme 2).



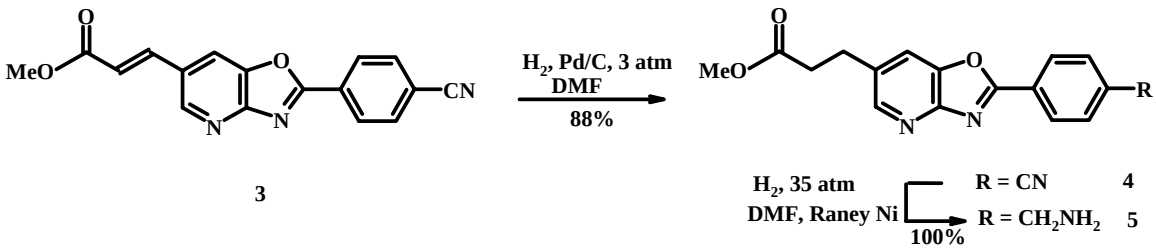
Scheme 2

Formation of 1,3-oxazolo derivative (**2**) was obtained by heating pyridine (**1**) and 4-cyanobenzoic acid in PPSE at 200°C in high yield (93 %) (Scheme 3).



Scheme 3

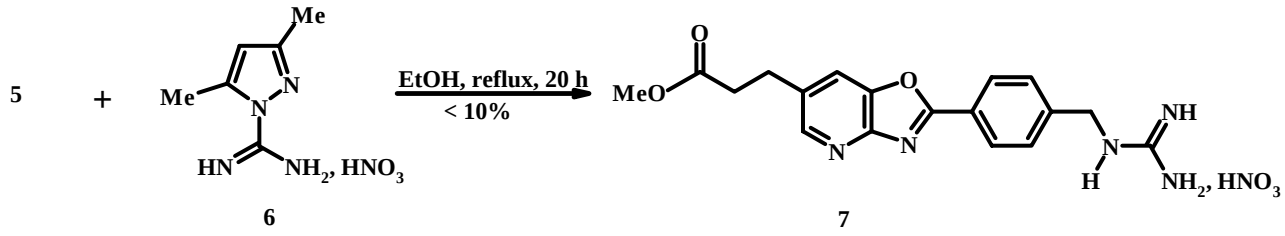
To introduce the acidic chain on the pyridine ring, a Heck reaction was performed between compound (**2**), palladium acetate (1%), tri-*o*-tolylphosphine and methyl acrylate in DMF at reflux, for 24 h. Compound (**3**) was obtained as an *E* isomer in 74% yield. Reduction of the double bond with hydrogen over palladium on carbon, under 3 atm, in DMF, for 2 days afforded compound (**4**) in 88% yield. Hydrogenation over Raney nickel of **4**, under 35 atm in DMF, allowed the quantitative reduction of the cyano group into the primary amino group (compound (**5**)), after 2 days (Scheme 4). This two-steps procedure gave higher yield and easy purification than the one-step reduction of both the nitrile group and ethylenic bond.



Scheme 4

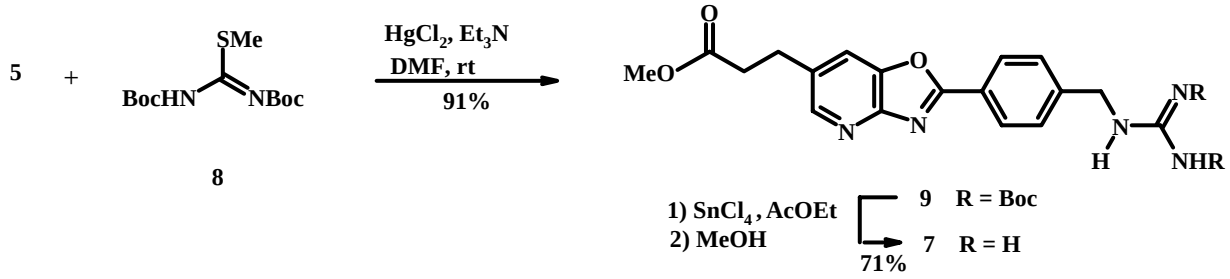
In order to reinforce the basic character of the amino group and to mimic arginine residue, which was involved in the binding with GPIIb/GPIIIa receptors, the guanylation of the amino group of **5** was attempted. The use of 3,5-dimethyl-1-pyrazolecarboximidamide (**6**)[13] gave an incomplete guanylation

reaction with difficulties to purify the desired compound (**7**), obtained as a nitrate salt (Scheme 5).



Scheme 5

Reaction of **5** with *N*,*N'*-bis(*tert*-butoxycarbonyl)thiourea[14,15] in presence of mercuric chloride and triethylamine gave a mixture of two monoBoc derivatives and one diBoc derivative (**9**) in 15 and 18% yields, respectively. Replacement of mercuric chloride with 2-chloro-*N*-methylpyridinium[16] did not much improved the yield of desired derivative (**9**) (22% yield), but the formation of monoBoc derivatives was not observed in this case. Nevertheless we succeed in obtaining the diBoc derivative (**9**) by using the method described by Miel and Rault.[17,18] Thus treatment of **5** with *N*,*N'*-bis(*tert*-butoxycarbonyl)-*S*-methylisothiourea (**8**) afforded **9** in excellent yield (91%) (Scheme 6).

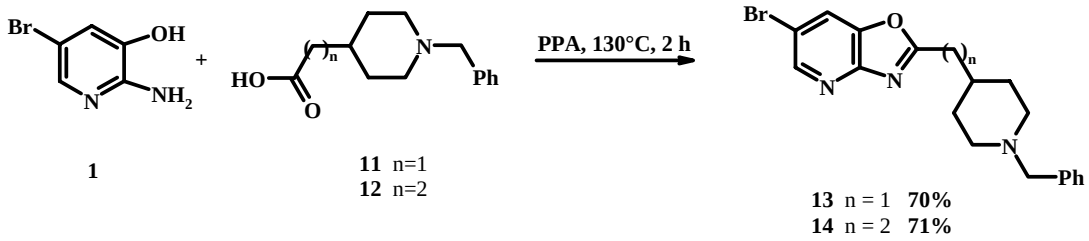


Scheme 6

Deprotection of the guanidino group of compound (**9**) was carried out using stannic chloride in ethyl acetate,[18] followed by treatment with methanol for 10 min. This procedure afforded directly in 71% yield **7** as hydrochloride salt, which was precipitated from the mixture by addition of ether.

In order to have more flexibility in the basic chain and also to modify the nature of the basic center, we have decided to replace the guanidino group by a piperidino group. An other factor which was also of interest was the distance between the oxazolo ring and the piperidino nitrogen atom. Thus we planned the synthesis of 2-(2-piperidin-4-yl-alkyl)oxazolo[4,5-*b*]pyridine. For introducing the alkylpiperidino chain we used the corresponding acids **(11)**[19,20] and (**12**); (basic hydrolysis of ethyl 3-(1-benzyl-4-piperidyl)propanoate (**10**) afforded acid (**12**). Oxazolo derivative (**13**) was obtained in only 22% yield, from **11**, by using PPSE at 200°C. The use of PPA instead of PPSE allowed us to obtain oxazolo compounds (**13**) and (**14**), in 70 and 71% yields, respectively (Scheme 7). Introduction of ethyl propenoate chain on the pyridine moiety was carried out using the same method as for **3**. Heck reaction

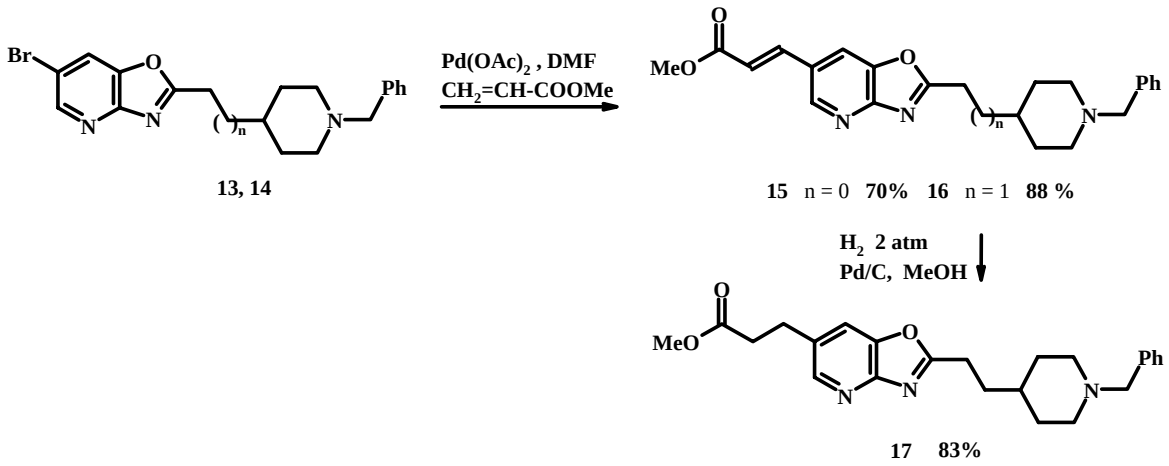
between compounds (**13**) or (**14**) and methyl acrylate in presence of palladium acetate afforded compounds (**15**) and (**16**), respectively in 70 and 88% yields.



1 **11** n=1 **12** n=2 **13** n = 1 **70%** **14** n = 2 **71%**

Scheme 7

The hydrogenation of the double bond of **16** was achieved with palladium, under 2 atm of hydrogen, to afford **17** in 83 % yield, without loss of the benzyl group (Scheme 8).

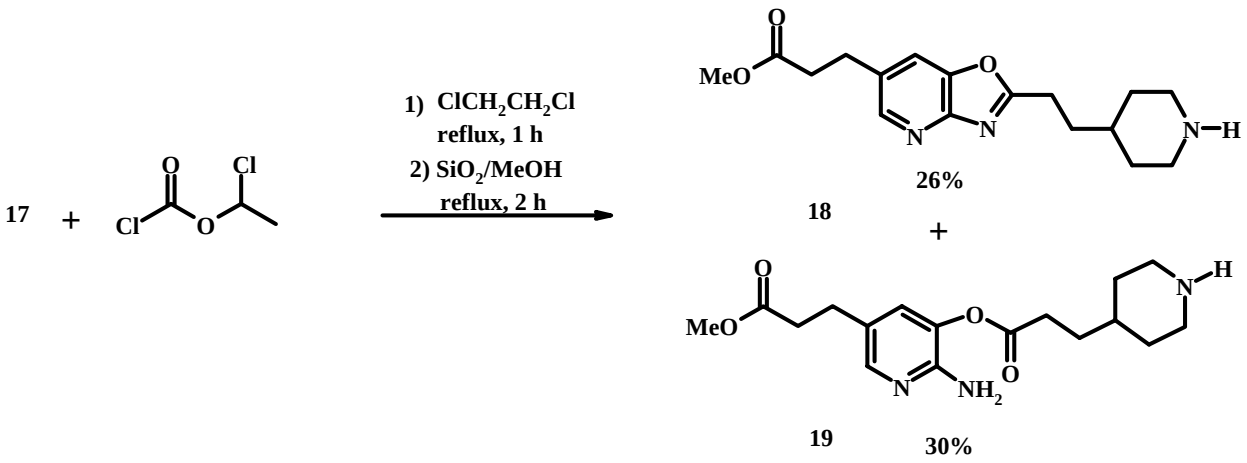


13, 14 **15** n = 0 **70%** **16** n = 1 **88 %** **17** **83%**

Scheme 8

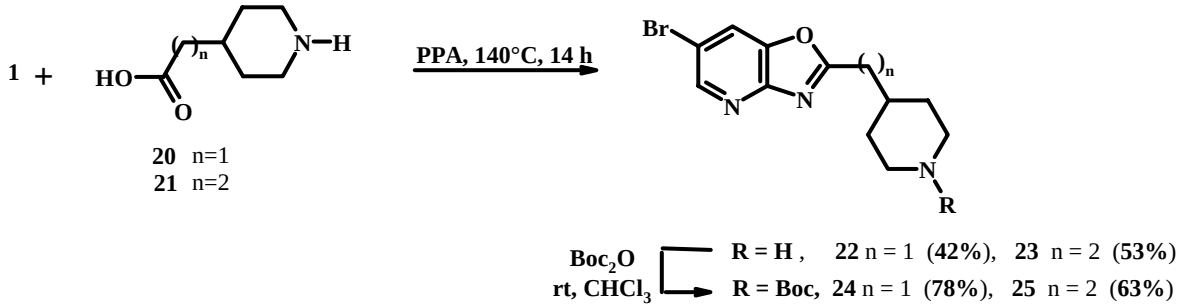
All attempts of deprotection of the nitrogen atom in compound (**17**) were unfruitful. Hydrogenolysis over palladium on carbon or $Pd(OH)_2$, in ethyl acetate or acetic acid leave **17** unchanged; a large excess of palladium on carbon afforded in an unreproductive manner compound (**18**) in 15-22% yield. Palladium with ammonium formate gave a degradation of the mixture. 1-Chloroethyl chloroformate[21-25] in 1,2-dichloroethane followed by methanolysis afforded a mixture of the expected debenzylated product (**18**), in 26% yield and compound (**19**), resulting of an oxazolo ring opening, in 30% yield (Scheme 9). Structure of **19** was in agreement, *inter alia*, with ^{13}C NMR data which indicated two CO (ester group) with chemical shift of 172.1 and 173.6 ppm respectively.

Benzyl group as protective group was inadequate, so we switched with the Boc group since we need to protect nitrogen atom for performing the Heck reaction; but in the oxazolo ring synthesis the Boc group did not survive during the PPA cyclization. Recently the reaction of 4-piperidinecarboxylic acid with 2-aminophenol have been reported[26] so we planned a such cyclization on 4-piperidinylacetic acid (**20**) or 3-(4-piperidinyl)propanoic acid (**21**), followed by introduction of the Boc group.



Scheme 9

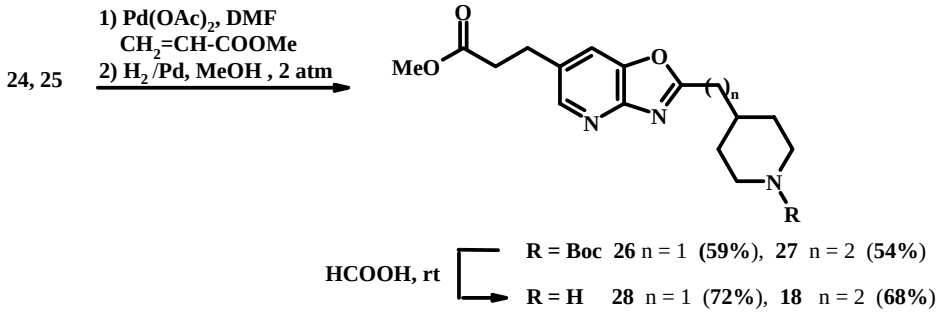
Reaction of **1** with acids (**20**) and (**21**) afforded the oxazolo derivatives (**22**) and (**23**), in 42 and 53 % yields, respectively (Scheme 10). These yields were lower than those obtained with the *N*-benzyl protected acids (**11)** and **(12**).



Scheme 10

Compounds (**22**) and (**23**) were reacted with Boc_2O in chloroform to give derivatives (**24**) and (**25**) respectively in 78 and 63 % yields. The desired compounds (**18**) and (**28**) were obtained using the same methodology reported for compound **(3**) (Scheme 11).

Heck reaction, with palladium acetate in DMF and methyl acrylate, on compounds (**24**) and (**25**), followed by hydrogenation of the double bond afforded compounds (**26)** and (**27**) in a two-steps overall yield of 59% and 54%, respectively. *N*-Boc protected derivatives (**24**) and (**25**) gave better yields in the Heck reaction than for compounds (**22**) and (**23**). Clean cleavage of the Boc group was carried out with formic acid at rt for 1 h, furnishing **18** and **28**, respectively in 68 and 72% yields as formate salt.



Scheme 11

This paper describes a new series of functionnalized oxazolo[4,5-*b*]pyridines with basic and acidic appendages. Since benzoxazole analogues have been reported[28] to possess activity as GPIIb/GPIIIa antagonists these compounds can be considered as potential antithrombotics.

EXPERIMENTAL

Melting points were determined using a Büchi MSP-20 melting point apparatus and were uncorrected. The IR spectra of compounds were recorded on a Perkin Elmer FT IR paragon 1000 spectrophotometer. NMR spectra were recorded at 300°K in $CDCl_3$ or DMSO-d_6 on a Bruker Avance DPX 250. Chemical shifts were expressed in parts per million and referenced to TMS. MS spectra were recorded on Perkin-Elmer SCIEX API 300 using ionspray methodology. Thin layer chromatography was performed on precoated plate of silica gel $60F_{254}$ (Merck) and the spots visualized using an ultraviolet lamp. Flash chromatography was conducted on Merck silica gel 60 (0.040 mm-0.063 mm) as the stationary phase; the ratio of eluents was indicated as volume. All air and moisture sensitive reactions were conducted under a prepurified argon atmosphere. Anhydrous solvents or reagents were transferred *via* syringe.

2-Amino-5-bromo-3-hydroxypyridine (1)

A suspension of 6-bromooxazolo[4,5-*b*]pyridin-2(3*H*)-one[11,12] (14.2 g, 66 mmol) in a 10% aqueous sodium hydroxide solution (160 mL) was refluxed for 8 h. After cooling, addition of 10% aqueous HCl solution gave a precipitate; the solid was filtered, washed with water and dried over phosphorus pentoxide to afford **1** (11.9 g, 94%), mp > 250 °C. IR (KBr) ν (cm^{-1}) : 3500-2900 (OH); 3450 and 3340 (NH_2) . ^{1}H NMR (DMSO-d_6 + D_2O) δ (ppm) 7.93 (d, 1H, H_4, *J* = 2.0 Hz); 7.46 (d, 1H, H_2, *J* = 2.0 Hz). MS (IS) : m/z 189, 191 (MH^+).

4-(6-Bromooxazolo[4,5-*b*]pyridin-2-yl)benzonitrile (2)

A solution of phosphorus pentoxide (15.77 g, 111 mmol) and hexamethyldisiloxane (40 mL, 185 mmol, 30.1 g) in dichloroethane (100 mL) was heated at reflux for 2 h. The solvent was evaporated and 2-amino-5-bromo-3-hydroxypyridine (**1**) (5 g, 26 mmol) and 4-cyanobenzoic acid (5.74 g, 39 mmol) were added to

the residue. The mixture was heated for 3 h at 200°C. After cooling, ice and water were added and the pH adjusted to 7-8 with a saturated aqueous solution of sodium hydrogencarbonate. The solid was filtered, washed several times with water and dried over phosphorus pentoxide to give **2** (7.4 g, 93%) as yellow solid, mp 239°C (EtOH). IR (KBr) ν (cm^{-1}) : 2236 (C≡N). ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88 (d, 2H, H_{arom}, *J* = 8.5 Hz); 8.12 (d, 1H, H_7, *J* = 2.0 Hz); 8.44 (d, 2H, H_{arom}, *J* = 8.5 Hz); 8.72 (d, 1H, H_5, *J* = 2.0 Hz).^{13}C NMR ($CDCl_3$) δ (ppm) 115.1 (C); 116.0 (C); 117.0 (C); 120.7 (CH); 127.6 (2 CH); 129.0 (C); 132.0 (2 CH); 142.6 (C); 147.9 (CH); 153.7 (C); 163.1 (O-C=N). MS (IS) : m/z 300, 302 (MH^+). Anal. Calcd for $C_{13}H_6N_3OBr$: C, 52.03; H, 2.02; N, 14.00. Found: C, 52.33; H, 2.14; N, 14.20.

Methyl (*E*)-3-[2-(4-Cyanophenyl)oxazolo[4,5-*b*]pyridin-6-yl]-2-propenoate (3)

Methyl acrylate (360 μL, 4 mmol, 344 mg), palladium acetate (8 mg, 0.033 mmol), tri-*o*-tolylphosphine (41 mg, 0.13 mmol), triethylamine (560 μL, 4 mmol, 404 mg), were successively added to the bromide (**2**) (1 g, 3.33 mmol) in DMF (40 mL). After refluxing for 24 h, the mixture was concentrated *in vacuo* and dichloromethane was added to the residue. The organic layer was washed with brine and dried over magnesium sulfate. Evaporation leave a residue which was purified by column chromatography (silica gel, eluent : CH_2Cl_2/ MeOH, 95 : 5) to give **3** (750 mg, 74 %) as yellow solid, mp 155 °C (decomp) ($MeOH/H_2O$). IR (KBr) ν (cm^{-1}) : 2221 (C≡N); 1734 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 3.86 (s, 3H, OCH_3); 6.69 (d, 1H, CO-CH=, *J* = 16.0 Hz); 6.84 (d, 1H, =CH, *J* = 16.0 Hz); 7.87 (dd, 2H, H_{arom}, *J* = 6.7 Hz, *J* = 1.7 Hz); 8.06 (d, 1H, H_7, *J* = 1.9 Hz); 8.45 (dd, 2H, H_{arom}, *J* = 6.7, 1.7 Hz); 8.78 (d, 1H, H_5, *J* = 1.9 Hz). ^{13}C NMR δ (ppm) 52.3 (OCH_3); 115.3 (C); 116.1 (CH); 117.2 (C); 120.5 (CH); 126.1 (C);127.7 (2 CH); 129.1 (C); 132.2 (2 CH); 141.3 (CH); 142.9 (C); 148.0 (CH); 153.8 (C); 163.3 (O-C=N), 170.2 (C=O). MS (IS) : m/z 306 (MH^+). Anal. Calcd for $C_{17}H_{11}N_3O_3$: C, 66.88; H, 3.63; N, 13.76. Found: C, 67.26; H, 3.49; N,13.57.

Methyl 3-[2-(4-Cyanophenyl)oxazolo[4,5-*b*]pyridin-6-yl]propanoate (4)

A suspension of compound (**3**) (600 mg, 1.97 mmol) and 10% Pd/C (60 mg) in DMF (60 mL) was shaken for 2 days at rt under 3 atm of hydrogen in a Parr apparatus. After filtration over a pad of celite the solvent was evaporated to leave a solid which was purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH, 97 : 3) to give **4** (530 mg, 88%) as yellow solid, mp 182 °C (MeOH). IR (KBr) ν (cm^{-1}) : 2228 (C≡N); 1737 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 2.73 (t, 2H, CH_2, *J* = 7.4 Hz); 3.14 (t, 2H, CH_2, *J* = 7.4 Hz); 3.68 (s, 3H, OCH_3); 7.80 (d, 1H, H_7, *J* = 1.5 Hz); 7.83 (d, 2H, H_{arom}, *J* = 8.3 Hz); 8.40 (d, 2H, H_{arom}, *J* = 8.3 Hz); 8.50 (d, 1H, H_5, *J* = 1.5 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 29.6 (CH_2); 36.8 (CH_2); 53.2 (OCH_3); 116.8 (C); 119.3 (C); 119.9 (CH); 129.7 (2 CH); 131.8 (C); 134.1 (2 CH); 135.7 (C); 144.7 (C); 149.2 (CH); 155.8 (C); 164.6 (O-C=N); 173.9 (C=O). MS (IS) : m/z 308 (MH^+). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67. Found: C, 66.35; H, 4.14; N, 13.51.

Methyl 3-{2-[4-(Aminomethyl)phenyl]oxazolo[4,5-*b*]pyridin-6-yl}propanoate (5)

A suspension of compound (**4**) (100 mg, 0.33 mmol) and Raney nickel (30 mg) in DMF (30 mL) was shaken under 35 atm of hydrogen. After 48 h at rt the mixture was filtered and the solvent evaporated. The residue was purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH / 30% NH_4OH, 100 : 10 : 1) to give **5** (100 mg, 100%) as yellow solid, mp 160 °C (decomp) (EtOH/H_2O). IR (KBr) ν (cm^{-1}) : 3345 and 3196 (NH_2); 1732 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.66 (br s, 2H, NH_2); 2.74 (t, 2H, CH_2, *J* = 7.4 Hz); 3.14 (t, 2H, CH_2, *J* = 7.4 Hz); 3.70 (s, 3H, OCH_3); 4.00 (s, 2H, NCH_2); 7.51 (d, 2H, H_{arom}, *J* = 8.2 Hz); 7.75 (d, 1H, H_7, *J* = 1.6 Hz); 8.28 (d, 2H, H_{arom}, *J* = 8.2 Hz); 8.45 (d, 1H, H_5, *J* = 1.6 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 28.7 (CH_2); 36.0 (CH_2); 46.6 (CH_2); 52.2 (OCH_3); 118.3 (CH); 125.4 (C); 128.0 (2 CH); 128.7 (2 CH); 133.5 (C); 141.9 (C); 147.3 (CH); 148.3 (C); 155.5 (C); 165.9 (O-C=N); 171.5 (C=O). MS (IS) : m/z 312 (MH^+). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.92; H, 5.44; N, 13.65.

Methyl 3-{2-[4-({[Amino(imino)methyl]amino}methyl)phenyl]oxazolo[4,5-*b*]pyridin-6-yl}propanoate (7) hydrochloride

To a solution of di-Boc derivative (**9**) (360 mg, 0.65 mmol) in ethyl acetate (5 mL), stannic tetrachloride (300 μL, 2.6 mmol, 677 mg) was added and the mixture stirred at rt for 2 h. Methanol was added and after stirring for 10 min the hydrochloride salt of **7** was precipitated by addition of ether. Filtration afforded **7, HCl** (180 mg, 71%) as white solid, mp 216 °C (decomp) (EtOH). IR (KBr) ν (cm^{-1}) : 3331 and 3165 (NH_2, NH); 1750 (C=O). ^{1}H NMR (CD_3OD) δ (ppm) 2.82 (t, 2H, CH_2, *J* = 7.4 Hz); 3.18 (t, 2H, CH_2, *J* = 7.4 Hz); 3.68 (s, 3H, OCH_3); 4.59 (d, 2H, NCH_2, *J* = 6.0 Hz); 7.61 (d, 2H, H_{arom}, *J* = 8.4 Hz); 8.14 (d, 1H, H_7, *J* = 1.7 Hz); 8.36 (d, 2H, H_{arom}, *J* = 8.4 Hz); 8.49 (d, 1H, H_5, *J* = 1.7 Hz). ^{13}C NMR (CD_3OD) δ (ppm) 25.7 (CH_2); 32.9 (CH_2); 42.2 (CH_2); 49.2 (OCH_3); 118.0 (CH); 123.3 (C); 125.7 (2 CH); 126.3 (2 CH); 132.9 (C); 139.9 (C); 143.6 (C); 143.8 (CH); 151.5 (C); 155.5 (N-C(NH)); 164.1 (O-C=N); 171.7 (C=O). MS (IS) : m/z 354 (MH^+). Anal. Calcd for $C_{18}H_{19}N_5O_3$, HCl: C, 55.46; H, 5.17; N, 17.96. Found: C, 55.06; H, 5.33; N, 18.17.

Methyl 3-(2-{4-[({[(*tert*-Butoxycarbonyl)amino][(*tert*-butoxycarbonyl)imino]methyl}-amino)methyl]phenyl}oxazolo[4,5-*b*]pyridin-6-yl)propanoate (9)

Triethylamine (360 μL, 2.56 mmol, 259 mg), *N*, *N'*-bis-(*tert*-butoxycarbonyl)-*S*-methylisothiourea (**8**)[17,18] (339 mg, 1.17 mmol), mercuric chloride (333 mg, 1.22 mmol) were added to a solution of amine (**5**) (400 mg, 1.28 mmol) in DMF (25 mL). After stirring for 4.5 h at rt ethyl acetate (50 mL) was added and the mixture was filtered over celite. The filtrate was washed successively with a 5% aqueous solution of sodium hydrogencarbonate, water and brine. The organic layer was dried over magnesium sulfate and evaporated. The residue was purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH,

99 : 1) to give **9** (590 mg, 91%) as white solid, mp 104 °C (decomp) (EtOH/H_2O). IR (KBr) ν (cm^{-1}) : 3322 (NH); 1742 (C=O); 1652 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.49 (s, 18H, 2 *t*-Bu); 2.73 (t, 2H, CH_2, *J* = 7.3 Hz); 3.14 (t, 2H, CH_2, *J* = 7.3 Hz); 3.69 (s, 3H, OCH_3); 4.75 (d, 2H, NCH_2, *J* = 5.4 Hz); 7.49 (d, 2H, H_{arom}, *J* = 8.2 Hz); 7.76 (d, 1H, H_7, *J* = 1.6 Hz); 8.28 (d, 2H, H_{arom}, *J* = 8.2 Hz); 8.45 (d, 1H, H_5, *J* = 1.6 Hz); 8.75 (br s, 1H, NH); 11.57 (sl, 1H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm) 28.4 (CH_2 and $C(CH_3)_3$); 28.7 ($C(CH_3)_3$); 35.9 (CH_2); 46.8 (CH_2); 52.2 (OCH_3); 82.8 (**C**$(CH_3)_3$); 83.9 (C); 118.6 (CH); 126.1 (C); 128.5 (2 CH); 128.8 (2 CH); 133.7 (C); 142.5 (C); 143.6 (C); 147.3 (CH); 153.6 (C); 155.4 (N-C=O); 156.7 (N-C=O); 163.8 (N-C-NBoc); 165.7 (O-C=N); 173.0 (C=O). MS (IS) : m/z 554.5 (MH^+). Anal. Calcd for $C_{28}H_{35}N_5O_7$: C, 60.75; H, 6.37; N, 12.65. Found: C, 60.48; H, 6.46; N, 12.80.

Ethyl 3-(1-Benzyl-4-piperidyl)propanoate (10)

Same procedure as for ethyl 2-(1-benzyl-4-piperidyl)acetate,[19] starting from ethyl 2-(4-piperidyl)propanoate (7.32 g, 39.5 mmol); oil; (8.72 g, 81%). IR (film) ν (cm^{-1}) : 1735 (C=O).^{1}H NMR ($CDCl_3$) δ (ppm) 1.21-1.27 (m, 6H, H_{3a-5a}, H_4, CH_3); 1.52-1.65 (m, 4H, H_{3b-5b} and **CH_2**-CH_2CO); 1.87-1.96 (m, 2H, H_{2a-6a}); 2.27-2.33 (m, 2H, CH_2CO); 2.84-2.89 (m, 2H, H_{2b-6b}); 3.47 (s, 2H, N-CH_2Ph); 4.12 (q, 2H, O-CH_2, *J* = 7.2 Hz); 7.21-7.29 (m, 5H, Ph). MS (IS) : m/z 276 (MH^+). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.42; H, 9.01; N, 5.13

3-(1-Benzyl-4-piperidyl)propanoic acid (12)

A solution of compound (**10**) (3.03 g, 11 mmol) in methanol (12 mL) and a 1N aqueous solution of sodium hydroxide (33 mL, 33 mmol) were stirred at rt for 12 h. After evaporation, the crude residue was dissolved in water and the pH adjusted to 4-5. Extraction with dichloromethane, drying over magnesium sulfate and evaporation leave a yellow solid, (2.25 g, 79%), mp 78 °C (EtOH). IR (KBr) ν (cm^{-1}) : 3500-2900 (OH); 1731 (C=O). ^{1}H NMR ($CDCl_3$ + D_2O) δ (ppm) 1.45-1.57 (m, 2H, H_{3a-5a}); 1.60-1.75 (m, 3H, H_4, **CH_2**-CH_2CO); 1.95-2.05 (m, 2H, H_{3b-5b}); 2.34-2.41 (m, 2H, CH_2CO); 2.99-3.09 (m, 2H, H_{2a-6a}); 3.47-3.53 (m, 2H, H_{2b-6b}); 4.34 (s, 2H, NCH_2-Ph); 7.45-7.62 (m, 5H, Ph). MS (IS) : m/z 248 (MH^+). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.50; H, 8.67; N, 5.49.

2-[(1-Benzyl-4-piperidinyl)methyl]-6-bromooxazolo[4,5-*b*]pyridine (13)

2-Amino-5-bromo-3-hydroxypyridine (**1**) (140 mg, 0.74 mmol) and acid (**11**)[20] (250 mg, 1.11 mmol) in PPA (1 g) were heated at 130°C for 2 h. After cooling, ice was added and the pH adjusted to 7-8 with a saturated solution of sodium hydrogencarbonate. Extraction with dichloromethane, drying over magnesium sulfate and evaporation leave a residue. Purification by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH, 95 : 5) afforded **13** (200 mg, 70%) as solid, mp 165 °C (EtOH/H_2O). IR (KBr) ν (cm^{-1}) : 1604 (C=N). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.38-1.54 (m, 2H, $H_{3'a-5'a}$); 1.74-1.80 (m, 2H, $H_{3'b-5'b}$); 1.80-2.10 (m, 3H, $H_{2'a-6'a}$, $H_{4'}$); 2.87-2.91 (m, 2H, $H_{2'b-6'b}$); 2.91 (d, 2H,CH_2C=N, *J* = 7.1 Hz); 3.51 (s,

2H, NCH_2Ph); 7.26-7.32 (m, 5H, Ph); 7.93 (d, 1H, H_7, *J* = 2.0 Hz); 8.59 (d, 1H, H_5, *J* = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 32.5 (2 CH_2); 34.9 (CH); 36.1 (CH_2); 53.7 (2 CH_2); 63.7 (CH_2); 115.8 (C); 121.3 (CH); 127.4 (CH); 128.6 (2 CH); 129.5 (2 CH); 138.7 (C); 143.5 (C); 147.6 (CH); 155.1 (C); 170.5 (O-C=N). MS (IS) : m/z 386, 388 (MH^+). Anal. Calcd for $C_{19}H_{20}N_3OBr$: C, 59.08; H, 5.22; N, 10.88. Found: C, 59.45; H, 5.36; N, 11.03.

2-[(1-Benzyl-4-piperidinyl)ethyl]-6-bromooxazolo[4,5-*b*]pyridine (14)

Same procedure as for **13** starting from acid (**12**) (1.96 g, 7.96 mmol). Solid, (1.51 g, 71%), mp 146 °C (EtOH/H_2O). IR (KBr) ν (cm^{-1}) : 1605 (C=N). ^1H NMR ($CDCl_3$) δ (ppm) 1.28-1.39 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.72-1.76 (m, 2H, $H_{3'b-5'b}$); 1.83-2.01 (m, 4H, $H_{2'a-6'a}$, CH_2-CH_2C=N); 2.89-2.94 (m, 2H, $H_{2'b-6'b}$); 3.01 (t, 2H, CH_2C=N, *J* = 7.5 Hz); 3.52 (s, 2H, NCH_2Ph); 7.23-7.33 (m, 5H, Ph); 7.94 (d, 1H, H_7, *J* = 2.0 Hz); 8.59 (d, 1H, H_5, *J* = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.8 (CH_2); 32.3 (2 CH_2); 33.3 (CH); 35.5 (CH_2); 54.0 (2 CH_2); 63.8 (CH_2); 115.7 (C); 121.2 (CH); 127.3 (CH); 128.5 (2 CH); 129.6 (2 CH); 138.8 (C); 143.5 (C); 147.6 (CH); 155.1 (C); 171.7 (O-C=N). MS (IS) : m/z 400 and 402 (MH^+). Anal. Calcd for $C_{20}H_{22}N_3OBr$: C, 60.01; H, 5.54; N, 10.50. Found: C, 59.85; H, 5.39; N, 10.41.

Methyl (*E*)-3-{2-[(1-Benzyl-4-piperidinyl)methyl]oxazolo[4,5-*b*]pyridin-6-yl}-2-propenoate (15)

Methyl acrylate (45 μL, 0.52 mmol, 44 mg), palladium acetate (6 mg, 0.026 mmol), tri-*o*-tolylphosphine (32 mg, 0.10 mmol), triethylamine (70 μL, 0.52 mmol, 52 mg), were sucessively added to the bromide (**13**) (100 mg, 0.26 mmol) in DMF (3 mL). After refluxing for 24 h, the mixture was concentrated *in vacuo* and dichloromethane was added to the residue. The organic layer was washed with brine and dried over magnesium sulfate. Evaporation leave a residue which was purified by column chromatography (silica gel, eluent : CH_2Cl_2/ MeOH, 95 : 5) to afford **15** (70 mg, 70 %) as brown solid, mp 152 °C (EtOH/H_2O). IR (KBr) ν (cm^{-1}) : 1710 (C=O); 1605 (C=N). ^1H NMR ($CDCl_3$) δ (ppm) 1.49-1.59 (m, 2H, $H_{3'a-5'a}$); 1.62-1.67 (m, 1H, $H_{4'}$); 1.78-1.83 (m, 2H, $H_{3'b-5'b}$); 2.01-2.09 (m, 2H, $H_{2'a-6'a}$); 2.91-2.96 (m, 2H, $H_{2'b-6'b}$); 2.97 (d, 2H, CH_2-C=N, *J* = 7.0 Hz); 3.54 (s, 2H, NCH_2Ph); 3.87 (s, 3H, OCH_3); 6.54 (d, 1H, =CH-CO, *J* = 16.0 Hz); 7.29-7.35 (m, 5H, Ph); 7.83 (d, 1H, CH=, *J* = 16.0 Hz); 7.93 (d, 1H, H_7, *J* = 1.8 Hz); 8.69 (d, 1H, H_5, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 32.4 (2 CH_2); 34.7 (CH); 35.9 (CH_2); 52.4 (OCH_3); 53.6 (2 CH_2); 63.5 (CH_2); 115.7 (CH); 120.3 (CH); 127.3 (CH); 127.5 (C); 128.4 (2 CH); 129.5 (2 CH); 138.6 (C); 141.4 (CH); 143.5 (C); 147.6 (CH); 155.5 (C); 168.5 (O-C=N); 172.4 (C=O). MS (IS) : m/z 392 (MH^+). Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.24; H, 6.45; N, 10.92.

Methyl (*E*)-3-{2-[(1-Benzyl-4-piperidinyl)ethyl]oxazolo[4,5-*b*]pyridin-6-yl}-2-propenoate (16)

Same procedure as for **15**, starting from bromide (**14**) (900 mg, 2.37 mmol). Brown solid, (850 mg, 88 %), mp 136 °C (EtOH/H_2O). IR (KBr) ν (cm^{-1}) : 1707 (C=O); 1603 (C=N). ^1H NMR ($CDCl_3$) δ (ppm) 1.40-

1.53 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.77-1.81 (m, 2H, $H_{3'b-5'b}$); 1.91-2.11 (m, 4H, $H_{2'a-6'a}$ and CH_2); 2.95-3.03 (m, 2H, $H_{2'b-6'b}$); 3.05 (t, 2H, CH_2-C=N, *J* = 7.5 Hz); 3.67 (s, 2H, N-CH_2Ph); 3.87 (s, 3H, OCH_3); 6.54 (d, 1H, =CH-CO, *J* = 16.0 Hz); 7.33-7.43 (m, 5H, Ph); 7.82 (d, 1H, CH=, *J* = 16.0 Hz); 7.93 (d, 1H, H_7, *J* = 1.6 Hz); 8.69 (d, 1H, H_5, *J* = 1.6 Hz). ^{13}C NMR($CDCl_3$) δ (ppm) 27.0 (CH_2); 32.3 (2 CH_2); 33.4 (CH_2); 35.5 (CH); 52.3 (OCH_3); 54.0 (2 CH_2); 63.8 (CH_2); 115.7 (CH); 119.9 (CH); 127.4 and 127.5 (CH and C); 128.5 (2 CH); 129.6 (2 CH); 138.7 (C); 141.5 (CH); 143.6 (C); 147.6 (CH); 157.8 (C); 167.1 (O-C=N); 172.9 (C=O). MS (IS) : m/z 406 (MH^+). Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.42; H, 6.58; N, 10.52.

Methyl 3-{2-[(1-Benzyl-4-piperidinyl)ethyl]oxazolo[4,5-*b*]pyridin-6-yl}propanoate (17)

A suspension of compound (**16**) (400 mg, 0.99 mmol) and 10% Pd/C (40 mg) in methanol (10 mL) was shaken under 2 atm of hydrogen in a Parr apparatus. After 24 h at rt the catalyst was filtered off and the solution evaporated. The residue was purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH, 95 : 5) to afford **17** (335 mg, 83%) as grey solid, mp 124 °C ($MeOH/H_2O$). IR (KBr) ν (cm^{-1}) : 1730 (C=O); 1607 (C=N). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.29-1.34 (m, 3H, $H_{3'a-5'a}$, $H_{4'}$); 1.70-1.74 (m, 2H, $H_{3'b-5'b}$); 1.80-1.88 (m, 2H, CH_2); 1.91-1.99 (m, 2H, $H_{2'a-6'a}$); 2.68 (t, 2H, CH_2, *J* = 7.5 Hz); 2.87-2.92 (m, 2H, $H_{2'b-6'b}$); 2.97 (t, 2H, CH_2, *J* = 7.5 Hz); 3.08 (t, 2H, CH_2, *J* = 7.5 Hz); 3.50 (s, 2H, NCH_2Ph); 3.66 (s, 3H, OCH_3); 7.23-7.31 (m, 5H, Ph); 7.63 (d, 1H, H_7, *J* = 1.7 Hz); 8.37 (d, 1H, H_5, *J* = 1.7 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.7 (CH_2); 28.5 (CH_2); 32.1 (2 CH_2); 33.3 (CH_2); 35.3 (CH); 35.9 (CH_2); 52.2 (OCH_3); 53.9 (2 CH_2); 63.7 (CH_2); 118.2 (CH); 127.4 (CH); 128.5 (2 CH); 129.7 (2 CH); 133.1 (C); 138.2 (C); 143.3 (C); 146.6 (CH); 154.8 (C); 170.7 (O-C=N); 173.0 (C=O). MS (IS) : m/z 408 (MH^+). Anal. Calcd for $C_{24}H_{29}N_3O_3$: C, 70.74; H, 7.17; N, 10.31. Found: C, 70.53; H, 6.99; N, 10.48.

Methyl 3-{2-[2-(4-Piperidinyl)ethyl]oxazolo[4,5-*b*]pyridin -6-yl}propanoate (18)

A suspension of compound (**17**) (50 mg, 0.12 mmol) and 10% Pd/C (130 mg) in acetic acid (2 mL) was shaken under 1 atm of hydrogen in a Parr apparatus. After 3 days at rt the catalyst was filtered and the solution evaporated. The residue was purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH / NH_4OH 30%, 100 : 20 : 2) to afford **18** (10 mg, 26%) as brown solid, mp 96 °C (decomp) ($MeOH/H_2O$). IR (KBr) ν (cm^{-1}) : 3429 (NH); 1727 (C=O); 1604 (C=N). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.26-1.35 (m, 2H, $H_{3'a-5'a}$); 1.47-1.55 (m, 1H, $H_{4'}$); 1.77-1.83 (m, 2H, $H_{3'b-5'b}$); 1.89 (t, 2H, CH_2, *J* = 7.3 Hz); 2.40 (br s, 1H, NH); 2.58 - 2.67 (m, 2H, $H_{2'a-6'a}$); 2.70 (t, 2H, CH_2, *J* = 7.5 Hz); 3.00 (t, 2H, CH_2, *J* = 7.5 Hz); 3.10 (t, 2H, CH_2, *J* = 7.3 Hz); 3.12-3.18 (m, 2H, $H_{2'b-6'b}$); 3.68 (s, 3H, OCH_3); 7.64 (d, 1H, H_7, *J* = 1.8 Hz); 8.39 (d, 1H, H_5, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.1 (CH_2); 28.1 (CH_2); 28.2 (2 CH_2); 33.4 (CH_2); 35.2 (CH); 35.6 (CH_2); 46.1 (2 CH_2); 51.8 (OCH_3); 117.8 (CH); 132.7 (C); 143.0 (C); 146.4

(CH); 154.6 (C); 170.2 (O-C=N); 172.6 (C=O). MS (IS) : m/z 318 (MH^+). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.68; H, 7.26; N, 13.14.

18, HCOOH was directly obtained from **27** using the same procedure as for compound (**28**); (100 mg, 68%); solid, mp 96 °C (MeOH).

Methyl 3-(6-Amino-5-{[3-(4-piperidyl)propanoyl]oxy}-3-pyridyl)propanoate (19)

To a solution of **17** (100 mg, 0.25 mmol) in refluxing dichloroethane (2 mL) was added ethyl 1-chloroethyl chloroformate (39 μL, 0.27 mmol, 38 mg). After stirring for 1 h at reflux, methanol (1 mL) and silica gel (100 mg) were added. After stirring for 2 h at reflux the mixture was evaporated and purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH / 30% NH_4OH, 100 : 10 : 1 then 100 : 20 : 2); two solids were obtained: **18**, (20 mg, 26%) and **19**, (25 mg, 30%), mp 174 °C (decomp) (AcOEt). IR (KBr) ν (cm^{-1}) : 3405 (NH_2); 3133 (NH); 1728 (C=O). ^{1}H NMR (CD_3OD) δ (ppm) 1.31-1.49 (m, 2H, $H_{3'a-5'a}$); 1.67-1.77 (m, 3H, piperidyl-**CH_2**, $H_{4'}$); 2.00-2.05 (m, 2H, $H_{3'b-5'b}$); 2.59 (t, 2H, piperidyl-CH_2-**CH_2**, *J* = 7.2 Hz); 2.68 (t, 2H, **CH_2**CH_2CO, *J* = 7.5 Hz); 2.92 (t, 2H, CH_2CO, *J* = 7.5 Hz); 2.96-3.08 (m, 2H, $H_{2'a-6'a}$); 3.39-3.45 (m, 2H, $H_{2'b-6'b}$); 3.70 (s, 3H, OCH_3); 7.22 (s, 1H, H_4); 7.79 (s, 1H, H_6). ^{13}C NMR (CD_3OD) δ (ppm) 26.0 (CH_2); 27.2 (CH_2); 28.8 (2 CH_2); 31.5 (CH_2); 33.4 (CH); 35.9 (CH_2); 44.2 (2 CH_2); 51.1 (OCH_3); 119.5 (CH); 125.8 (CH); 139.4 (C); 142.5 (C); 149.6 (C); 172.1 (C=O); 173.6 (C=O). MS (IS) : m/z 336 (MH^+). Anal. Calcd for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.52; H, 7.67; N, 12.44.

3-(4-Piperidyl)propanoic Acid (21)[29,30]

Ethyl 3-[1-(*tert*-Butoxycarbonyl)-4-piperidyl]propanoate

To a solution of ethyl 3-(4-piperidyl)propanoate (3.66 g, 19.8 mmol) in dioxane / water (1 : 1) (40 mL) were added triethylamine (8.3 mL, 59,2 mmol, 5.99 g) and di-*tert*-butyloxycarbonyl carbonate (6.03 g, 27.6 mmol). After stirring for 96 h at rt the solvent was evaporated to leave a residue; water was added and the mixture extracted with ethyl acetate. Drying over magnesium sulfate and evaporation leave an oil; (5.5 g, 97%). IR (film) ν (cm^{-1}) : 1735 (C=O); 1695 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.03-1.18 (m, 2H, H_{3a-5a}); 1.27 (t, 3H, CH_3, *J* = 7.1 Hz); 1.37-1.42 (m, 1H, H_4); 1.46 (s, 9H, *t*-Bu); 1.58-1.64 (m, 2H, CH_2); 1.68-1.78 (m, 2H, H_{3b-5b}); 2.33 (t, 2H, CH_2-CO, *J* = 7.4 Hz); 2.62-2.72 (m, 2H, H_{2a-6a}); 4.06-4.12 (m, 2H, H_{2b-6b}); 4.15 (q, 2H, O-CH_2, *J* = 7.1 Hz). MS (IS) : m/z 286 (MH^+).

3-[1-(*tert*-Butoxycarbonyl)-4-piperidyl]propanoic Acid

A solution of ethyl 3-[1-(*tert*-butoxycarbonyl)-4-piperidyl]propanoate (5 g, 17.5 mmol) in ethanol (20 mL) and aqueous 1N sodium hydroxide (52.5 mL, 52.5 mmol) was stirred for 12 h at rt; after evaporation, the residue was taken in water. Washing with ether was followed by acidification of the aqueous layer; extraction with ether gave after drying over magnesium sulfate and evaporation a white solid; (4.1 g,

91%), mp 123 °C. IR (KBr) ν (cm^{-1}) : 2900-3500 (OH); 1726 (C=O); 1623 (C=O). ^{1}H NMR ($CDCl_3$ + D_2O) δ (ppm) 1.02-1.18 (m, 2H, H_{3a-5a}); 1.36-1.41 (m, 1H, H_4); 1.45 (s, 9H, *t*-Bu); 1.56-1.62 (m, 2H, CH_2); 1.63-1.68 (m, 2H, H_{3b-5b}); 2.39 (t, 2H, -CH_2-CO, *J* = 7.4 Hz); 2.62-2.72 (m, 2H, H_{2a-6a}); 4.06-4.11 (m, 2H, H_{2b-6b}). MS (IS) : m/z 258 (MH^+).

3-(4-Piperidyl)propanoic Acid

A solution of 3-[1-(*tert*-butoxycarbonyl)-4-piperidyl]propanoic acid (700 mg, 2.72 mmol) in dioxan (5 mL) containing 4N HCl was stirred for 1 h at 0°C. Ethyl acetate was added to the mixture and a solid precitated. After filtration, a white solid (525 mg, 99 %) was obtained, mp 242 °C (lit.,[28] 244 °C). IR (KBr) ν (cm^{-1}) : 3500-2900 (OH); 3426 (NH); 1723 (C=O). ^{1}H NMR (CD_3OD) δ (ppm) 1.12-1.28 (m, 3H, H_{3a-5a}, H_4); 1.33-1.42 (m, 2H, CH_2); 1.63-1.68 (m, 2H, H_{3b-5b}); 2.15 (t, 2H, CH_2-CO, *J* = 7.4 Hz); 2.70-2.82 (m, 2H, H_{2a-6a}); 3.16-3.21 (m, 2H, H_{2b-6b}). ^{13}C NMR (CD_3OD) δ (ppm) 28.7 (2 CH_2); 30.7 (CH_2); 30.9 (CH_2); 33.3 (CH); 44.2 (2 CH_2); 174.5 (C=O). MS (IS) : m/z 158 (MH^+).

6-Bromo-2-(4-piperidinylmethyl)oxazolo[4,5-*b*]pyridine (22)

A mixture of 2-amino-5-bromo-3-hydroxypyridine (**1**) (490 mg, 2.60 mmol) and acid (**20**)[27] (560 mg, 3.90 mmol) in PPA (4 g) was stirred for 14 h at 140°C. After cooling, ice was added and pH adjusted to 12 with 5% aqueous sodium hydroxide. Extraction with dichloromethane, drying over magnesium sulfate and evaporation leave a residue which was purified by column chromatography (silica gel, eluent : CH_2Cl_2 / MeOH /30% NH_4OH, 100 : 20 : 2) to give **22** (320 mg, 42%) as grey solid, mp 184°C (EtOH). IR (KBr) ν (cm^{-1}) : 3373 (NH); 1601 (C=N). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.20-1.35 (m, 2H, $H_{3'a-5'a}$); 1.73-1.77 (m, 2H, $H_{3'b-5'b}$); 1.88-1.94 (m, 1H, $H_{4'}$); 2.23 (br s, 1H, NH); 2.58-2.68 (m, 2H, $H_{2'a-6'a}$); 2.88 (d, 2H, CH_2-C=N, *J* = 7.1 Hz); 3.04-3.09 (m, 2H, $H_{2'b-6'b}$); 7.92 (d, 1H, H_7, *J* = 2.0 Hz); 8.56 (d, 1H, H_5, *J* = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 34.0 (2 CH_2); 35.8 (CH); 37.1 (CH_2); 49.2 (2 CH_2); 116.3 (C); 121.8 (CH); 144.0 (C); 148.1 (CH); 155.5 (C); 170.8 (O-C=N). MS (IS) : m/z 296 and 298 (MH^+). Anal. Calcd for $C_{12}H_{14}N_3OBr$: C, 48.67; H, 4.76; N, 14.19. Found: C, 48.32; H, 4.70; N, 14.35.

6-Bromo-2-[2-(4-piperidinyl)ethyl]oxazolo[4,5-*b*]pyridine (23)

Same procedure as for **22** starting from acid (**21**)[29,30] (526 mg, 2.72 mmol). Solid, (300 mg, 53%), mp 166 °C (EtOH). IR (KBr) ν (cm^{-1}) : 3429 (NH); 1600 (C=N). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.09-1.25 (m, 2H, $H_{3'a-5'a}$); 1.42-1.52 (m, 1H, $H_{4'}$); 1.72-1.77 (m, 2H, $H_{3'b-5'b}$); 1.85 (q, 2H, **CH_2**-CH_2-C=N, *J* = 7.5 Hz); 2.53-2.63 (m, 3H, $H_{2'a-6'a}$, NH); 3.01 (t, 2H, CH_2-C=N, *J* = 7.5 Hz); 3.05-3.11 (m, 2H, $H_{2'b-6'b}$); 7.93 (d, 1H, H_7, *J* = 2.2 Hz); 8.59 (d, 1H, H_5, *J* = 2.2 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.2 (CH_2); 33.4 (2 CH_2); 33.5 (CH_2); 35.6 (CH); 46.6 (2 CH_2); 115.4 (C); 120.9 (CH); 143.2 (C); 147.3 (CH); 154.7 (C); 171.3 (O-C=N). MS (IS) : m/z 310, 312 (MH^+). Anal. Calcd for $C_{13}H_{16}N_3OBr$: C, 50.34; H, 5.20; N, 13.55. Found: C, 50.31; H, 5.04; N, 13.72.

***tert*-Butyl 4-[2-(6-Bromooxazolo[4,5-*b*]pyridin-2-yl)methyl]-1-piperidinecarboxylate (24)**

A solution of compound (**22**) (250 mg, 0.84 mmol), diisopropylethylamine (320 µL, 1.85 mmol, 240 mg), di-*tert*-butyl dicarbonate (370 mg, 1.69 mmol) in chloroform (5 mL) was stirred for 24 h at rt. Dichloromethane and water were added to the mixture; the organic layer was then washed with water. Drying of the organic extracts over magnesium sulfate and evaporation leave a residue which was purified by column chromatography (silica gel, eluent : EtOAc / petroleum ether, 1 : 1) to give **24** (250 mg, 78%) as grey solid, mp 163 °C (EtOAc). IR (KBr) ν (cm^{-1}) : 1687 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.26-1.45 (m, 2H, $H_{3'a-5'a}$); 1.50 (s, 9H, *t*-Bu); 1.75-1.81 (m, 2H, $H_{3'b-5'b}$); 2.13-2.22 (m, 1H, $H_{4'}$); 2.70-2.79 (m, 2H, $H_{2'a-6'a}$); 2.92 (d, 2H, CH_2-C=N, *J* = 7.1 Hz); 4.10-4.15 (m, 2H, $H_{2'b-6'b}$); 7.96 (d, 1H, H_7, *J* = 2.0 Hz); 8.59 (d, 1H, H_5, *J* = 2.0 Hz). ^{13}C NMR δ (ppm) 28.8 ($C(CH_3)_3$); 32.2 (2 CH_2); 35.0 (CH); 36.0 (CH_2); 44.1 (2 CH_2); 79.8 (C); 115.9 (C); 121.4 (CH); 143.5 (C); 147.7 (CH); 155.0 (C); 155.1 (C=O); 169.9 (O-C=N). MS (IS) : 396, 398 (MH^+). Anal. Calcd for $C_{17}H_{22}N_3O_3Br$: C, 51.53; H, 5.60; N, 10.60. Found: C, 51.91; H, 5.78; N, 10.43.

***tert*-Butyl 4-[2-(6-Bromopyrido oxazolo[4,5-*b*]pyridin-2-yl)ethyl]-1-piperidinecarboxylate (25)**

Same procedure as for **24**, starting from **23** (300 mg, 0.97 mmol). Solid, (250 mg, 63%), mp 145 °C (EtOAc). IR (KBr) ν (cm^{-1}) : 1686 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.13-1.26 (m, 2H, $H_{3'a-5'a}$); 1.45 (s, 9H, *t*-Bu); 1.49-1.58 (m, 1H, $H_{4'}$); 1.70-1.77 (m, 2H, $H_{3'b-5'b}$); 1.87 (q, 2H, **CH_2**-CH_2C=N, *J* = 7.4 Hz); 2.63-2.72 (m, 2H, $H_{2'a-6'a}$); 3.01 (t, 2H, CH_2-C=N, *J* = 7.4 Hz); 4.08-4.14 (m, 2H, $H_{2'b-6'b}$); 7.94 (d, 1H, H_7, *J* = 2.0 Hz); 8.59 (d, 1H, H_5, *J* = 2.0 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.6 (CH_2); 28.8 ($C(CH_3)_3$); 32.1 (2 CH_2); 33.2 (CH_2); 35.7 (CH); 44.1 (2 CH_2); 79.7 (C); 115.8 (C); 121.3 (CH); 143.5 (C); 147.6 (CH); 155.0 (C); 155.2 (N-C=O); 171.4 (O-C=N). MS (IS) : 410 and 412 (MH^+) . Anal. Calcd for $C_{18}H_{24}N_3O_3Br$: C, 52.69; H, 5.90; N, 10.24. Found: C, 52.31; H, 5.74; N, 10.40.

***tert*-Butyl 4-{2-[6-(3-Methoxy-3-oxopropyl] oxazolo[4,5-*b*]pyridin-2-yl}methyl)-1-piperidine-carboxylate (26)**

tert-Butyl 4-({6-[(*E*)-3-Methoxy-3-oxo-1-propenyl]oxazolo[4,5-*b*]pyridin-2-yl}methyl)-1-piperidinecarboxylate

Same procedure as for **15** starting from **24** (300 mg, 0.79 mmol). Solid, (290 mg, 95%), mp 157 °C (MeOH). IR (KBr) ν (cm^{-1}) : 1711 (C=O); 1688 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.12-1.28 (m, 2H, $H_{3'a-5'a}$); 1.45 (s, 9H, *t*-Bu); 1.75-1.81 (m, 2H, $H_{3'b-5'b}$); 2.16-2.20 (m, 1H, $H_{4'}$); 2.69-2.79 (m, 2H, $H_{2'a-6'a}$); 2.94 (d, 2H, CH_2-C=N, *J* = 7.1 Hz); 3.83 (s, 3H, OCH_3); 4.08-4.14 (m, 2H, $H_{2'b-6'b}$); 6.51 (d, 1H, =CH-CO, *J* = 16.0 Hz); 7.79 (d, 1H, CH=, *J* = 16.0 Hz); 7.92 (d, 1H, H_7, *J* = 1.9 Hz); 8.67 (d, 1H, H_5, *J* = 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 28.8 ($C(CH_3)_3$); 32.2 (2 CH_2); 35.1 (CH); 36.2 (CH_2); 44.2 (2 CH_2); 52.4 (OCH_3); 79.9 (C); 115.8 (CH); 120.1 (CH); 127.7 (CH); 141.4 (CH); 143.5 (C); 147.7 (CH); 155.1 (C);

157.7 (N-C=O); 167.1 (O-C=N); 171.1 (C=O). MS (IS) : m/z 402 (MH^+). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78 N, 10.47. Found: C, 62.56; H, 6.72; N, 10.35.

A suspension of *tert*-butyl 4-({6-[(*E*)-3-methoxy-3-oxo-1-propenyl]oxazolo[4,5-*b*]pyridin-2-yl}methyl)-1-piperidinecarboxylate (290 mg, 0.72 mmol) and 10% Pd/C (30 mg) in methanol (7 mL) was shaken under 2 atm of hydrogen in a Parr apparatus. After 24 h at rt, the catalyst was filtered and the solution evaporated. The residue was purified by column chromatography (silica gel, eluent : EtOAc / petroleum ether, 4 : 6) to afford **26** (180 mg, 62%) as grey solid, mp 148 °C (MeOH/H_2O). IR (KBr) ν (cm^{-1}) : 1730 (C=O); 1687 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.17-1.32 (m, 2H, $H_{3'a-5'a}$); 1.45 (s, 9H, *t*-Bu); 1.75-1.81 (m, 2H, $H_{3'b-5'b}$); 2.16-2.20 (m, 1H, $H_{4'}$); 2.70 (t, 2H, CH_2, *J* = 7.4 Hz); 2.72 - 2.79 (m, 2H, $H_{2'a-6'a}$); 2.91 (d, 2H, CH_2, *J* = 7.1 Hz); 3.10 (t, 2H, CH_2, *J* = 7.4 Hz); 3.68 (s, 3H, OCH_3); 4.09-4.14 (m, 2H, $H_{2'b-6'b}$); 7.65 (d, 1H, H_7, *J* = 1.9 Hz); 8.40 (d, 1H, H_5, *J* = 1.9 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 28.5 (2 CH_2); 28.8 ($C(CH_3)_3$); 32.2 (2 CH_2); 35.1 (CH); 36.0 (CH_2); 44.1 (2 CH_2); 52.2 (OCH_3); 79.8 (C); 118.2 (CH); 133.2 (C); 143.3 (C); 146.9 (CH); 154.9 (C); 155.1 (N-C=O); 169.0 (O-C=N); 173.0 (C=O). MS (IS) : m/z; 404 (MH^+). Anal. Calcd for $C_{21}H_{29}N_3O_5$: C, 62.51; H, 7.24; N, 10.11. Found: C, 62.90; H, 7.33; N, 10.02.

tert-Butyl 4-{2-[6-(3-Methoxy-3-oxopropyl]oxazolo[4,5-*b*]pyridin-2-yl}ethyl)-1-piperidine-carboxylate (27)

tert-Butyl (4-({6-[(*E*)-3-Methoxy-3-oxo-1-propenyl]oxazolo[4,5-*b*]pyridin-2-yl}ethyl)-1-piperidine-carboxylate

Same procedure as for **16**, starting from **25** (340 mg, 0.83 mmol). A brown solid (310 mg, 90%) was obtained, mp 138 °C (MeOH). IR (KBr) ν (cm^{-1}) : 1709 (C=O); 1662 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.15-1.26 (m, 2H, $H_{3'a-5'a}$); 1.47 (s, 9H, *t*-Bu); 1.50-1.58 (m, 1H, $H_{4'}$); 1.71-1.77 (m, 2H, $H_{3'b-5'b}$); 1.90 (q, 2H, $\mathbf{CH_2}$-CH_2-C=N, *J* = 7.5 Hz); 2.64-2.74 (m, 2H, $H_{2'a-6'a}$); 3.05 (t, 2H, $\mathbf{CH_2}$-C=N, *J* = 7.5 Hz); 3.85 (s, 3H, OCH_3); 4.08-4.14 (m, 2H, $H_{2'b-6'b}$); 6.53 (d, 1H, =CH-CO, *J* = 16.0 Hz); 7.81 (d, 1H, CH=, *J* = 16.0 Hz); 7.93 (d, 1H, H_7, *J* = 1.8 Hz); 8.68 (d, 1H, H_5, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.3 (CH_2); 28.4 ($C(CH_3)_3$); 31.7 (2 CH_2); 32.8 (CH_2); 35.3 (CH); 43.8 (2 CH_2); 51.9 (OCH_3); 79.3 (C); 115.3 (CH); 119.5 (CH); 127.1 (CH); 141.0 (CH); 143.1 (C); 147.2 (CH); 154.7 (C); 157.3 (N-C=O); 166.6 (O-C=N); 172.1 (C=O). MS (IS) : m/z 416.5 (MH^+). Anal. Calcd for $C_{22}H_{29}N_3O_5$: C, 63.60; H, 7.04; N, 10.11. Found: C, 63.23; H, 6.89; N, 10.22.

A suspension of *tert*-butyl (4-({6-[(*E*)-3-methoxy-3-oxo-1-propenyl] oxazolo[4,5-*b*]pyridin-2-yl}ethyl)-1-piperidinecarboxylate (350 mg, 0.84 mmol) and 10% Pd/C (35 mg) in methanol (8 mL) was stirred under 2 atm of hydrogen in a Parr apparatus. After 24 h at rt the catalyst was filtered and the solution evaporated. The residue was purified by column chromatography (silica gel, eluent : EtOAc / petroleum ether, 4 : 6) to give **27** (210 mg, 60%) as grey solid, mp 130 °C (MeOH/H_2O). IR (KBr) ν (cm^{-1}) : 1727

(C=O); 1694 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.11-1.20 (m, 2H, $H_{3'a-5'a}$); 1.47 (s, 9H, *t*-Bu); 1.51-1.58 (m, 1H, $H_{4'}$); 1.72-1.76 (m, 2H, $H_{3'b-5'b}$); 1.87 (q, 2H, **C**H_2-CH_2-C=N, *J* = 7.5 Hz); 2.71 (t, 2H, C**H**$_2$-CH_2CO, *J* = 7.5 Hz); 2.58-2.68 (m, 2H, $H_{2'a-6'a}$); 3.02 (t, 2H, **C**H_2-C=N, *J* = 7.5 Hz); 3.11 (t, 2H, **C**H_2-CO, *J* = 7.5 Hz); 3.69 (s, 3H, OCH_3); 4.09-4.14 (m, 2H, $H_{2'b-6'b}$); 7.66 (d, 1H, H_7, *J* = 1.8 Hz); 8.41 (d, 1H, H_5, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.5 (CH_2); 28.5 (CH_2); 28.8 ($C(CH_3)_3$); 32.1 (2 CH_2); 33.3 (CH_2); 35.6 (CH); 36.0 (CH_2); 44.2 (2 CH_2); 52.2 (OCH_3); 79.7 (C); 118.2 (CH); 133.1 (C); 143.3 (C); 146.7 (CH); 154.9 (C); 155.2 (N-C=O); 170.4 (O-C=N); 173.0 (C=O). MS (IS) : m/z 418.5 (MH^+). Anal. Calcd for $C_{22}H_{31}N_3O_5$: C, 63.29; H, 7.48; N, 10.06. Found: C, 63.56; H, 7.67; N, 10.24.

Methyl 3-[2-(4-Piperidinylmethyl)oxazolo[4,5-*b*]pyridin-6-yl]propanoate (28), HCOOH salt

A solution of compound (**26**) (160 mg, 0.37 mmol) in formic acid (3 mL) was stirred for 1 h at rt. Evaporation of the solvent under *vacuo* leave a solid which was crystallized in ether to give **28** (100 mg, 72%), mp 95 °C (decomp). IR (KBr) ν (cm^{-1}) : 3500-2900 (OH); 3426 (NH); 1730 (C=O). ^{1}H NMR ($CDCl_3$) δ (ppm) 1.77-1.86 (m, 2H, $H_{3'a-5'a}$); 2.05-2.11 (m, 2H, $H_{3'b-5'b}$); 2.34-2.40 (m, 1H, $H_{4'}$); 2.74 (t, 2H, **C**H_2-CH_2CO, *J* = 7.3 Hz); 2.97-3.05 (m, 4H, $H_{2'a-6'a}$, CH_2-C=N); 3.14 (t, 2H, CH_2-CO, *J* = 7.3 Hz); 3.49-3.54 (m, 2H, $H_{2'b-6'b}$); 3.71 (s, 3H, OCH_3); 7.69 (s, 1H, H_7); 8.42 (br s, 2H, H_5, HC=O); 9.65 (br s, 2H, NH, OH). ^{13}C NMR ($CDCl_3$) δ (ppm) 28.5 (CH_2); 28.9 (CH_2); 33.1 (2 CH_2); 35.3 (CH); 36.0 (CH_2); 43.8 (2 CH_2); 52.2 (OCH_3); 118.5 (CH); 133.6 (C); 143.4 (C); 147.0 (CH); 154.6 (C); 168.1 (HC=O); 168.2 (O-C=N); 173.0 (C=O). MS (IS) : m/z 304 (MH^+). Anal. Calcd for $C_{16}H_{21}N_3O_3$, HCOOH: C, 58.43; H, 6.63; N, 12.03. Found: C, 58.79; H, 6.78; N, 12.15.

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