Synthesis of 2(3*H*)-Benzoxazolone and 2(3*H*)-Benzothiazolone Derivatives as Potential Beta-3-Adrenergic Receptor Ligands (part 2)

J. F. Delhomel, S. Yous*, P. Depreux and D. Lesieur

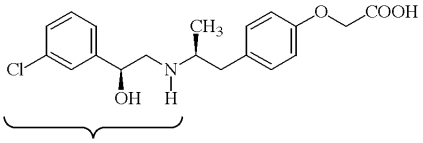
Laboratoire de Chimie Pharmaceutique, Faculté des Sciences Pharmaceutiques et Biologiques,
3, rue du Professeur Laguesse - BP 83 - 59006 Lille cedex- France
Received October 4, 2000

Adrenoceptors beta-3-subtype mediate lipolysis and in the search for potential beta−3−adrenergic receptors agonists for the treatment of obesity, we designed new arylethanolamines (structures **4**, **5**) and aryloxypropanolamines (structures **6**, **7**) derived from 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone.

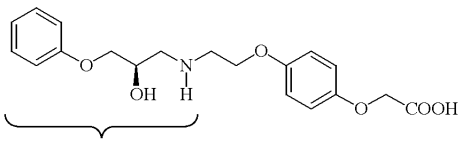
J. Heterocyclic Chem., **38**, 633 (2001).

Beta-3-adrenoreceptor agonists are potential therapeutic agents for the treatment of metabolic disorders such as obesity and diabetes [1-3].

A large number of beta-3-adrenergic receptor agonists belong to two general structural classes (Figure 1): *i.e.*, arylethanolamine, *e.g.*, **1** [4] and aryloxypropanolamine, *e.g.*, **2** [5,6]. Hence, efforts are underway in our laboratory to synthesize novel, potent and selective beta-3-adrenergic receptor agonists. In a recent work [7] we describe the preparation of compound **3** (Figure 2) which includes two 2(3*H*)-benzoxazolone heterocycles:



Arylethanolamine (**1**)



Aryloxypropanolamine (**2**)

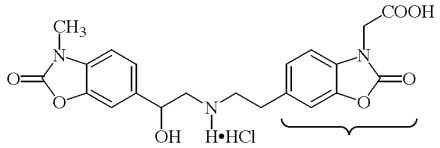
Figure 1

the first one filling the place of the phenyl ring of the phenylethanolamine moiety, the second one bearing the acidic functionality of the arylalkyl group.

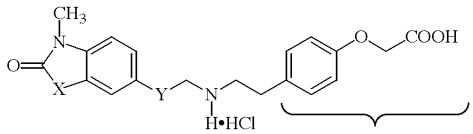
In the present study, our aim was to further investigate the role of the 2(3*H*)-benzoxazolone unit bearing the acidic functionality. So we replaced this moiety by a phenoxyacetic group and prepared the two benzoxazolinonic and benzothiazolinonic series of arylethanolamines (**4**-**5**) and aryloxypropanolamines (**6**-**7**) (Figure 2).

Compounds listed in figure 2 were synthesized according to Schemes 1-4. Synthesis of amines **10** and **11** (Scheme 1) started with the commercially available 2-(4-hydroxyphenyl)ethylamine hydrochloride which was *N*-Boc protected [8] and allowed to react with ethylbromoacetate in the presence of potassium carbonate to yield **9** (94%). Cleavage of the *tert*-butyloxycarbonyl protecting group occurred in acidic medium leading to **10** with 90% yield. Condensation with benzaldehyde followed by reduction with sodium borohydride gave the secondary amine **11** (55%).

The preparation of racemic arylethanolamines **4** and **5** was described in Scheme 2. Starting from 6-(2-bromoacetyl)-3-methyl-2(3*H*)-benzoxazolone (**12**) [9,10] and its sulphured analogue **13** [11], a substitution reaction with the secondary amine **11** provide compounds **14** and **15** with 67% and 60% yield. Cleavage of the benzyl group by 1-chloroethyl chloroformate and methanol [12] afforded **16** and **17** with 70% and 75% yield, respectively. Then, reduction of the ketone with sodium borohydride in



[2(3*H*)-Benzoxazolon-3-yl] acetic acid moiety (**3**)

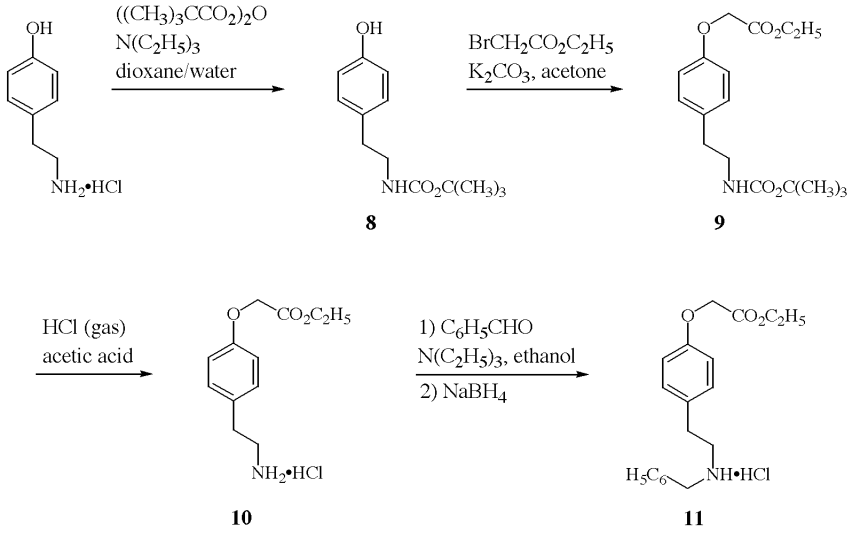


Phenoxyacetic acid moiety (**4-7**)

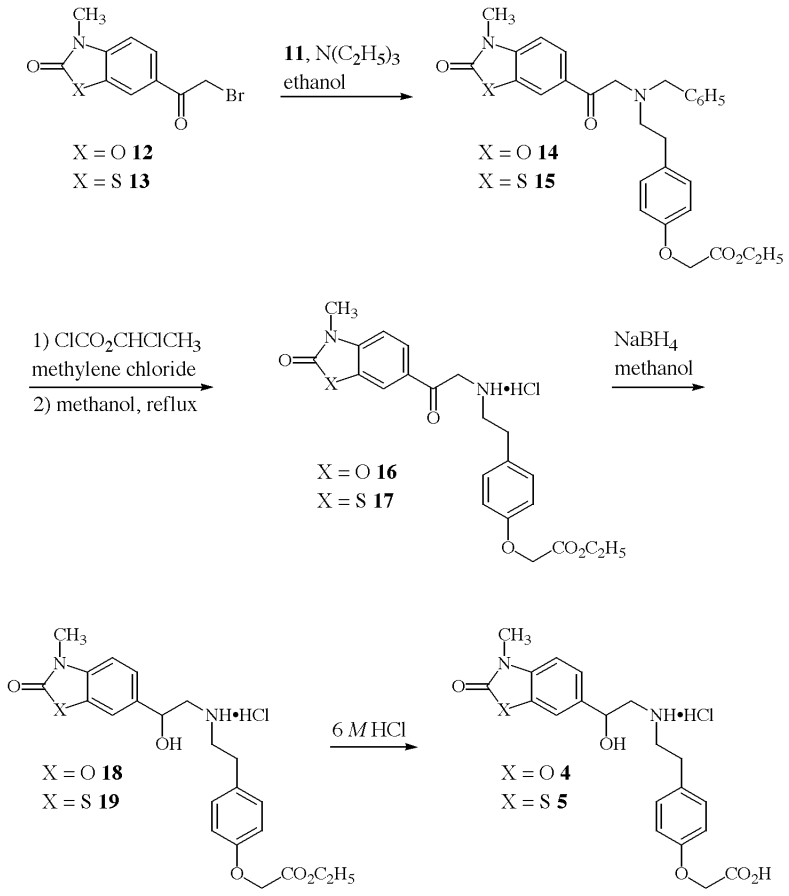
Compound	X	Y
4	O	—CH(OH)—
5	S	—CH(OH)—
6	O	—OCH_2CH(OH)—
7	S	—OCH_2CH(OH)—

Figure 2

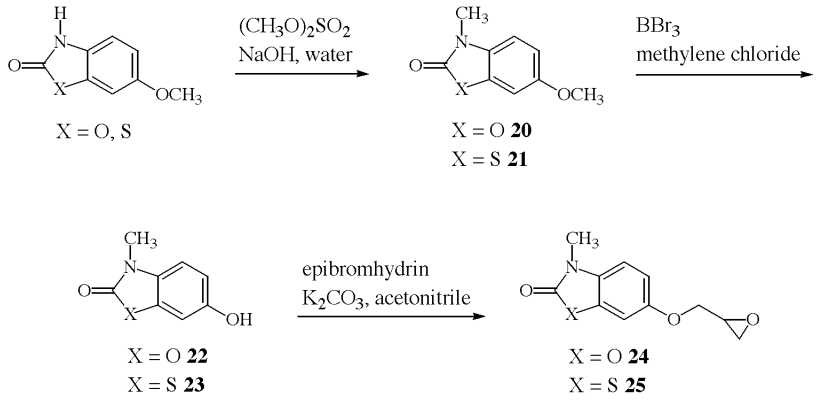
Scheme 1



Scheme 2



Scheme 3

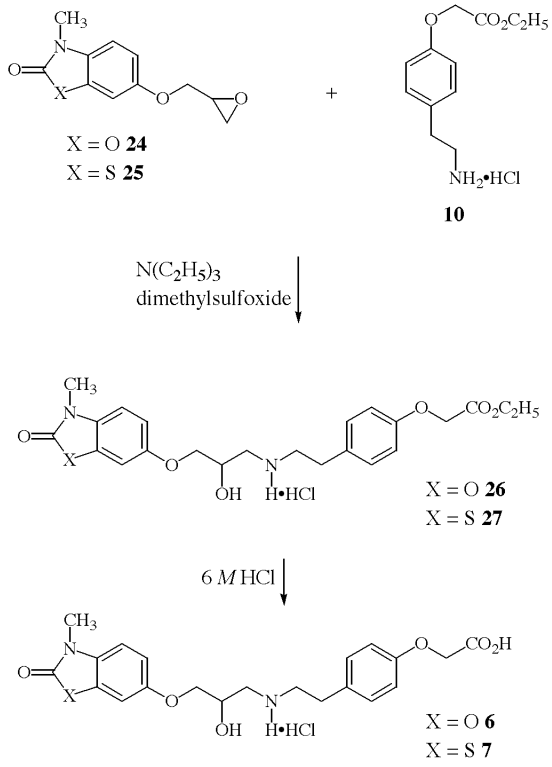


methanol followed by hydrolysis of the ester functions with 6 *M* hydrochloric acid respectively provided the corresponding acid derivatives **4** and **5**.

On the other hand, the epoxide **24** was prepared in a three step procedure starting from 6-methoxy-2(3*H*)-benzoxazolone (Scheme 3) which was successively treated with dimethylsulfate in basic medium to afford compound **20** in 87% yield and with boronetribromide in methylene chloride to yield **22** (76%). Condensation of epibromhydrin with the phenolic compound **22** in the presence of potassium carbonate provides **24** with 85% yield. Starting from 6-methoxy-2(3*H*)-benzothiazolone [13] a similar pathway was used for the sulphured analogue **25** with comparable yields (Scheme 3).

The nucleophilic substitution of **24** and **25** by the primary amine **10** lead to the racemic esters **26** and **27** which after hydrolysis provided the acid derivatives **6** and **7** with an overall yield of 32% and 38%, respectively (Scheme 4).

Scheme 4



EXPERIMENTAL

Melting points were determined using a Büchi 530 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 297 spectrometer and the ^{1}H nmr spectra were recorded using a Brücker AC 300 spectrometer. Chemical shifts are reported in ppm with tetramethylsilane as internal standard. All compounds were found homogenous in TLC (Merck silicagel 60F254, ethyl acetate/acetone, 60/40, v/v). Elemental analyses were performed by the "Service Central de Microanalyses", CNRS, Vernaison, France and are within ± 0.4% of the calculated values. Compounds **12** and **13** were synthesized according to the previously described procedures [9-11].

[2-(4-Hydroxyphenyl)ethyl]carbamic Acid *tert*-Butyl Ester (**8**).

Triethylamine (19 ml, 100 mmol) was added to a solution of 2-(4-hydroxyphenyl)ethylamine hydrochloride (17.4 g, 100 mmol) in 200 ml of a mixture of dioxane-water (3/1). Di-*tert*-butyldicarbonate (21.8 g, 100 mmol) was then added. The mixture was stirred for 2 hours at room temperature, the solvent was evaporated and the residue taken off with ethylacetate. The organic phase was washed with 0.5 *M* hydrochloric acid, water, dried and evaporated under vacuum. The residue was recrystallized from cyclohexane to give **8** in 91% yield: mp: 71-72 °C; ir (potassium bromide): ν 3400 (OH), 1670 (2(3*H*)-benzoxazolone CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.45 (s, 9H, $C(CH_3)_3$), 2.70 (t, 2H, CH_2CH_2N, J = 6.40 Hz), 3.35 (m, 2H, CH_2CH_2N), 4.64 (br s, 1H, NH

exchangeable with D_2O), 6.40 (br s, 1H, OH exchangeable with D_2O), 6.79 (d, 2H, H_2, H_6, J*ortho* = 8.90 Hz), 7.00 (d, 2H, H_3, H_5, J*ortho* = 8.90 Hz).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.01; H, 8.05; N, 5.75.

[4-(2- *tert*-Butoxycarbonylaminoethyl)phenoxy]acetic Acid Ethyl Ester (**9**).

To a stirred solution of **8** (23.7 g, 100 mmol) in anhydrous acetone (100 ml) was added K_2CO_3 (24 g, 170 mmol) and ethylbromoacetate (30 ml, 140 mmol). After 12 hours of stirring under reflux the reaction mixture was filtered . The filtrate was evaporated under vacuum, the residue taken off with ethylacetate and the organic layer was washed with a 0.5 *M* solution of sodium hydroxyde, with water, dried and evaporated under vacuum. The residue was recrystallized from cyclohexane to give **9** in 94% yield: mp 45-47 °C; ir (potassium bromide): ν 3340 (NH), 1750 (ester CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, 3H, OCH_2CH_3, J = 6.90 Hz), 1.45 (s, 9H, $C(CH_3)_3$), 2.70 (t, 2H, CH_2CH_2N, J = 6.30 Hz), 3.40 (m, 2H, CH_2CH_2N), 4.25 (q, 2H, OCH_2CH_3, J = 6.90 Hz), 4.64 (br s, 1H, NH exchangeable with D_2O), 4.75 (s, 2H, $COCH_2$), 6.85 (d, 2H, H_2, H_6, J*ortho* = 8.80 Hz), 7.15 (d, 2H, H_3, H_5, J*ortho* = 8.80 Hz).

Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.34; H, 8.00; N, 4.44.

[4-(2-Aminoethyl)phenoxy]acetic Acid Ethyl Ester Hydrochloride (**10**).

Compound **9** (32.3 g, 100 mmol) was dissolved in a saturated hydrochloric acid solution of acetic acid (55 ml). After stirring for 1 hour at room temperature, the precipitate was filtered, washed with diethylether and recrystallized from absolute ethanol to give **10** in 90% yield: mp: 162-164 °C; ir (potassium bromide): ν 1750 (ester CO) cm^{-1} ; ^1H nmr (deuteriochloroform) δ (ppm) 1.21 (t, 3H, OCH_2CH_3, J = 7.10 Hz), 2.85 (t, 2H, CH_2CH_2N, J = 8.30 Hz), 2.95 (m, 2H, CH_2CH_2N), 4.18 (q, 2H, OCH_2CH_3, J = 7.10 Hz), 4.75 (s, 2H, $COCH_2$), 6.88 (d, 2H, H_2, H_6, J*ortho* = 8.10 Hz), 7.35 (d, 2H, H_3, H_5, J*ortho* = 8.10 Hz), 8.19 (br s, 3H, NH_3^+ exchangeable with D_2O).

Anal. Calcd. for $C_{12}H_{17}NO_3$•HCl: C, 55.49; H, 6.98; N, 5.39. Found: C, 55.42; H, 6.99; N, 5.42.

[4-(2-Benzylaminoethyl)phenoxy]acetic Acid Ethyl Ester Hydrochloride (**11**).

To a solution of **10** (1 g, 3.8 mmol) in ethanol (20 ml) was added triethylamine (0.7 ml, 5 mmol) and benzaldehyde (0.5 ml, 5 mmol). After stirring for 30 minutes, sodium borohydride (0.22 g, 5.80 mmol) was added portionwise and stirring was continued for 14 hours. Ethanol was evaporated and the residue taken off with water (300 ml). The aqueous mixture was extracted with ethylacetate. The organic phase was dried and evaporated under vacuum. The residue was treated with diethylether saturated with gaseous hydrochloric acid. The precipitate was filtered, washed with diethylether and recrystallized from absolute ethanol to give **11** in 55% yield: mp 202-204 °C; ir (potassium bromide): ν 1750 (ester CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide) δ (ppm) 1.21 (t, 3H, OCH_2CH_3, J = 7.10 Hz), 2.70 (t, 2H, CH_2CH_2N, J = 7.10 Hz), 3.00 (m, 2H, CH_2CH_2N), 4.10 (s, 2H, $C_6H_5CH_2$), 4.20 (q, 2H, OCH_2CH_3, J = 7.10 Hz), 4.80 (s, 2H, $COCH_2$), 6.80 (d, 2H, H_2, H_6, J*ortho* = 8.50 Hz), 7.10 (d, 2H, H_3, H_5, J*ortho* = 8.50 Hz), 7.50 (m, 5H, C_6H_5), 9.70 (br s, 2H, NH_2^+ exchangeable with D_2O).

Anal. Calcd. for $C_{19}H_{23}NO_3$•HCl: C, 65.23; H, 6.91; N, 4.00. Found: C, 65.29; H, 6.95; N, 3.97.

[4-(2-{Benzyl-[2-(3-methyl-2(3*H*)-benzoxazolon-6-yl)-2-oxoethyl]amino} ethyl)phenoxy)acetic Acid Ethyl Ester (**14**).

To a solution of **11** (7 g, 20 mmol) in ethanol (20 ml) were added successively triethylamine (7 ml, 0.05 mol), and compound **12** (5.6 g, 21 mmol). The reaction mixture was stirred at reflux for 20 minites and then evaporated *in vacuo*. The residue was taken up with ethylacetate. The organic layer was washed with water, dried over magnesium sulfate, and evaporated. Recrystallization from ethanol gave **14** in 67% yield: mp 79-80 °C; ir (potassium bromide): ν 1750 (2(3*H*)-benzoxazolone and ester CO), 1660 (ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6-sulfoxide): δ (ppm) 1.21 (t, 3H, CH_2CH_3, J = 7.10 Hz), 2.70 (m, 4H, CH_2CH_2), 3.38 (s, 3H, NCH_3), 3.75 (s, 2H, $NCH_2C_6H_5$), 3.95 (s, 2H, NCH_2CO), 4.16 (q, 2H, CH_2CH_3, J = 7.10 Hz), 4.70 (s, 2H, CH_2O), 6.75 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.30 Hz), 7.00 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.30 Hz), 7.26-7.31 (m, 6H, H_4, H_{benzyl}), 7.78 (d, 1H, H_7, J*meta* = 2.35 Hz), 7.85 (dd, 1H, H_5, J*ortho* = 8.20 Hz, J*meta* = 2.35 Hz).

Anal. Calcd. for $C_{29}H_{30}N_2O_6$; C, 69.31; H, 6.02; N, 5.57. Found: C, 69.19; H, 5.95; N, 5.58.

[4-(2-{Benzyl-[2-(3-methyl-2(3*H*)-benzothiazolon-6-yl)-2-oxoethyl]amino}ethyl)phenoxy)acetic Acid Ethyl Ester (**15**).

The reaction was carried out as described for compound **14**. Recrystallization from ethanol gave **15** in 60% yield: mp 164-165 °C; ir (potassium bromide): ν 1750 (ester CO), 1670 (2(3*H*)-benzothiazolone and ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6-sulfoxide): δ 1.21 (t, 3H, CH_2CH_3, J = 7.00 Hz), 3.06 (m, 2H, CH_2CH_2N), 3.35 (m, 2H, CH_2CH_2N), 3.47 (s, 3H, NCH_3), 4.16 (q, 2H, CH_2CH_3, J = 7.00 Hz), 4.55 (m, 2H, $CH_2C_6H_5$), 4.74 (s, 2H, CH_2O), 5.15 (m, 2H, NCH_2CO), 6.88 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.10 Hz), 7.18 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.10 Hz), 7.44-7.70 (m, 6H, H_4, H_{benzyl}), 8.03 (dd, 1H, H_5, J*ortho* = 8.40 Hz, J*meta* = 2.36 Hz), 8.38 (d, 1H, H_7, J*meta* = 2.36 Hz), 10.67 (br s, 1H, NH^+ exchangeable with D_2O).

Anal. Calcd. for $C_{29}H_{30}N_2O_5S$•HCl ; C, 62.75; H, 5.72; N, 5.05. Found: C, 62.52; H, 5.72; N, 5.03.

(4-{2-[2-(3-Methyl-2(3*H*)-benzoxazolon-6-yl)-2-oxoethylamino]ethyl} phenoxy)acetic Acid Ethyl Ester Hydrochloride (**16**).

To a solution of **14** (2 g, 4 mmol) in methylene chloride (20 ml) was added 1-chloroethyl chloroformate (0.65 ml, 6 mmol). After heating at reflux for 1 hour, methylene chloride was evaporated and methanol (40 ml) was added. The reaction mixture was stirred at reflux for 30 minutes. After cooling the precipitate was filtered and recrystallized from ethanol to give **16** in 70% yield: mp 248-249 °C; ir (potassium bromide): ν 1760 (2(3*H*)-benzoxazolone and ester CO), 1670 (ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide) δ (ppm) 1.22 (t, 3H, CH_2CH_3, J = 7.10 Hz), 3.04 (m, 2H, CH_2CH_2N), 3.18 (m, 2H, CH_2CH_2N), 3.41 (s, 3H, NCH_3), 4.18 (q, 2H, CH_2CH_3, J = 7.10 Hz), 4.76 (s, 2H, CH_2O), 4.82 (m, 2H, NCH_2CO), 6.91 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.50 Hz), 7.21 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.50 Hz), 7.48 (d, 1H,

H_4, J*ortho* = 8.40 Hz), 7.91 (d, 1H, H_7, J*meta* = 2.34 Hz), 7.95 (dd, 1H, H_5, J*ortho* = 8.40 Hz, J*meta* = 2.34 Hz), 9.51 (br s, 2H exchangeable with D_2O).

Anal. Calcd. for $C_{22}H_{24}N_2O_6$•HCl: C, 58.86; H, 5.61; N, 6.24. Found: C, 58.58; H, 5.70; N, 6.09.

(4-{2-[2-(3-Methyl-2(3*H*)-benzothiazolon-6-yl)-2-oxoethylamino]ethyl} phenoxy)acetic Acid Ethyl Ester Hydrochloride (**17**).

The reaction was carried out as described for compound **16**. Recrystallization from ethanol gave **17** in 75% yield: mp 238-242 °C; ir (potassium bromide): ν 1750 (ester CO), 1670 (2(3*H*)-benzothiazolone and ketone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide) δ (ppm) 1.22 (t, 3H, CH_2CH_3, J = 7.10 Hz), 3.00 (m, 2H, CH_2CH_2N), 3.17 (m, 2H, CH_2CH_2N), 3.48 (s, 3H, NCH_3), 4.17 (q, 2H, CH_2CH_3, J = 7.10 Hz), 4.76 (s, 2H, CH_2O), 4.82 (m, 2H, NCH_2CO), 6.91 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.50 Hz), 7.21 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.50 Hz), 7.52 (d, 1H, H_4, J*ortho* = 8.50 Hz), 8.05 (dd, 1H, H_5, J*ortho* = 8.40 Hz, J*meta* = 2.30 Hz), 8.41 (d, 1H, H_7, J*meta* = 2.30 Hz), 9.44 (br s, 2H exchangeable with D_2O).

Anal. Calcd. for $C_{22}H_{24}N_2O_5S$•HCl: C, 56.83; H, 5.42; N, 6.02. Found: C, 56.88; H, 5.81; N, 6.20.

(4-{2-[(2-Hydroxy-2-(3-methyl-2(3*H*)-benzoxazolon-6-yl)ethylamino]ethyl} phenoxy)acetic Acid Ethyl Ester Hydrochloride (**18**).

Sodium borohydride (0.19 g, 5 mmol) was added over a period of 5 minutes to a suspension of **16** (0.9 g, 2 mmol) in methanol (20 ml). The reaction mixture was then stirred over 20 minutes at room temperature. The solvent was evaporated *in vacuo*., and 1 *M* hydrochloric acid (10 ml) was added to the residue. The resulting precipitate was filtered and recrystallized from ethanol to give **18** in 70% yield: mp 237-238 °C; ir (potassium bromide): ν 3340 (OH), 1750 (2(3*H*)-benzoxazolone and ester CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.20 (t, 3H, CH_2CH_3, J = 7.10 Hz), 2.92-3.12 (m, 6H, $CH_2CH_2NCH_2$), 3.49 (s, 3H, NCH_3), 4.16 (q, 2H, CH_2CH_3, J = 7.10 Hz), 4.75 (s, 2H, CH_2O), 5.00 (m, 1H, C*H*OH), 6.26 (br s, 1H, OH exchangeable with D_2O), 6.89 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.60 Hz), 7.17 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.60 Hz), 7.26-7.35 (m, 3H, H_4, H_5, H_7), 8.92 (br s, 2H exchangeable with D_2O).

Anal. Calcd. for $C_{22}H_{26}N_2O_6$•HCl: C, 58.60; H, 6.03; N, 6.21. Found: C, 58.34; H, 5.94; N, 6.12.

(4-{2-[(2-Hydroxy-2-(3-methyl-2(3*H*)-benzothiazolon-6-yl)ethylamino]ethyl}phenoxy)acetic Acid Ethyl Ester Hydrochloride (**19**).

The reaction was carried out as described for compound **18**. Recrystallization from ethanol gave **19** in 88% yield: mp 175-176 °C; ir (potassium bromide): ν 3350 (OH), 1750 (ester CO), 1700 (2(3*H*)-benzothiazolone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.21 (t, 3H, CH_2CH_3, J = 7.10 Hz), 2.96-3.14 (m, 6H, $CH_2CH_2NCH_2$), 3.41 (s, 3H, NCH_3), 4.16 (q, 2H, CH_2CH_3, J = 7.10 Hz), 4.75 (s, 2H, CH_2O), 5.07 (m, 1H, C*H*OH), 6.33 (br s, 1H, OH exchangeable with D_2O), 6.89 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.60 Hz), 7.17 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.60 Hz), 7.33 (d, 1H, H_4, J*ortho* = 8.40 Hz), 7.42 (dd, 1H, H_5, J*ortho* = 8.40 Hz, J*meta* = 2.30 Hz), 7.70 (d, 1H, H_7, J*meta* = 2.30 Hz), 9.26 (br s, 2H exchangeable with D_2O).

Anal. Calcd. for $C_{22}H_{26}N_2O_5S$•HCl: C, 56.58; H, 5.83; N, 6.00. Found: C, 56.57; H, 5.80; N, 6.01.

(4-{2-[(2-Hydroxy-2-(3-methyl-2(3*H*)-benzoxazolon-6-yl)ethylamino]ethyl}phenoxy)acetic Acid Hydrochloride (**4**).

Compound **18** (0.5 g, 1.1 mol) was dissolved in 6 *M* hydrochloric acid (50 ml). The solution was heated under reflux for 30 minutes, and then cooled to 4 °C to get a precipitate that was filtered and recrystallized from ethanol to give **4** in 61% yield: mp 242-243 °C; ir (potassium bromide): ν 1750 (2(3*H*)-benzoxazolone CO), 1710 (carboxylic acid CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide) δ (ppm) 2.92-3.14 (m, 6H, $CH_2CH_2NCH_2$), 3.35 (s, 3H, NCH_3), 4.65 (s, 2H, CH_2O), 5.01 (m, 1H, C*H*OH), 6.30 (br s, 1H, OH exchangeable with D_2O), 6.87 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.50 Hz), 7.17 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.50 Hz), 7.27-7.37 (m, 3H, H_4, H_5, H_7), 9.00 (br s, 2H exchangeable with D_2O).

Anal. Calcd. for $C_{20}H_{22}N_2O_6$•HCl: C, 56.81; H, 5.48; N, 6.42. Found: C, 56.58; H, 5.39; N, 6.55.

(4-{2-[(2-Hydroxy-2-(3-methyl-2(3*H*)-benzothiazolon-6-yl)-ethylamino]ethyl}phenoxy)acetic Acid Hydrochloride (**5**).

The reaction was carried out as described for compound **4**. Recrystallization from ethanol gave **5** in 66% yield: mp 187-191 °C; ir (potassium bromide): ν 1770 (carboxylic acid CO), 1670 (2(3*H*)-benzothiazolone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.98-3.14 (m, 6H, $CH_2CH_2NCH_2$), 3.41 (s, 3H, NCH_3), 4.65 (s, 2H, CH_2O), 5.07 (m, 1H, C*H*OH), 6.32 (br s, 1H, OH exchangeable with D_2O), 6.87 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 7.80 Hz), 7.17 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 7.80 Hz), 7.32 (d, 1H, H_4, J*ortho* = 8.10 Hz), 7.40 (dd, 1H, H_5, J*ortho* = 8.10 Hz, J*meta* = 2.25 Hz), 7.70 (d, 1H, H_7, J*meta* = 2.25 Hz), 9.30 (br s, 2H exchangeable with D_2O), 13.00 (br s, 1H, COOH exchangeable with D_2O).

Anal. Calcd. for $C_{20}H_{22}N_2O_5S$•HCl ; C, 54.73; H, 5.28; N, 6.38 Found: C, 54.80; H, 5.32; N, 6.07.

6-Methoxy-3-methyl-2(3*H*)-benzoxazolone (**20**).

6-Methoxy-2(3*H*)-benzoxazolone (16.4 g, 100 mmol) was dissolved in a 0.2 *N* aqueous solution of sodium hydroxide (0.5 L). This solution was stirred at room temperature and dimethylsulfate (14.5 ml, 150 mmol) was added dropwise. Just after the addition was complete, a precipitate appeared; the suspension was stirred 4 hours at room temperature and filtered. The solid was washed with water and recrystallized from ethanol to give **20** in 87% yield: mp 96-97 °C; ir (potassium bromide): ν 1760 (2(3*H*)-benzoxazolone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.40 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 6.58-6.65 (m, 3H, H_4, H_5, H_7).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.07; N, 7.82. Found: C, 60.73; H, 5.10; N, 7.93.

6-Methoxy-3-methyl-2(3*H*)-benzothiazolone (**21**).

The reaction was carried out as described for compound **20**. Recrystallization from ethanol gave **21** in 76% yield: mp 78-79 °C; ir (potassium bromide): ν 1670 (2(3*H*)-benzothiazolone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.40 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.88 (dd, 1H, H_5, J*ortho* = 8.70 Hz, J*meta* = 2.20 Hz), 6.94 (d, 1H, H_4, J*ortho* = 8.70 Hz), 7.00 (d, 1H, H_7, J*meta* = 2.20 Hz).

Anal. Calcd. for $C_9H_9NO_2S$: C, 55.36; H, 4.65; N, 7.17. Found: C, 55.29; H, 4.54; N, 6.90.

6-Hydroxy-3-methyl-2(3*H*)-benzoxazolone (**22**).

To a solution of **20** (8.95 g, 50 mmol) in methylene chloride (80 ml) was added dropwise borane tribromide (9.45 ml, 100 mmol) at 0 °C and under nitrogen atmosphere. The mixture was stirred for 5 hours at room temperature, poured into water and extracted with methylene chloride. The organic phase was washed with water, dried over magnesium sulfate, filtered and evaporated. Recrystallization of the residue from ethanol gave **22** in 82% yield: mp 203-204 °C; ir (potassium bromide): ν 3280 (OH), 1750 (2(3*H*)-benzoxazolone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.35 (s, 3H, NCH_3), 6.65 (dd, 1H, H_5, J*ortho* = 7.70 Hz, J*meta* = 1.54 Hz), 6.75 (d, 1H, H_7, J*meta* = 1.54 Hz), 6.92 (d, 1H, H_4, J*ortho* = 7.70 Hz), 9.45 (br s, 1H, OH exchangeable with D_2O).

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; H, 4.28; N, 8.48. Found: C, 58.29; H, 4.35; N, 8.56.

6-Hydroxy-3-methyl-2(3*H*)-benzothiazolone (**23**).

The reaction was carried out as described for compound **22**. Recrystallization from ethanol gave **23** in 88% yield: mp 182-183 °C; ir (potassium bromide): ν 3220 (OH), 1645 (2(3*H*)-benzothiazolone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.35 (s, 3H, NCH_3), 6.80 (d, 1H, H_5, J*ortho* = 8.60 Hz), 7.05 (d, 1H, H_7, J*meta* = 2.10 Hz), 7.10 (d, 1H, H_4, J*ortho* = 8.60 Hz), 9.45 (br s, 1H, OH exchangeable with D_2O).

Anal. Calcd. for $C_8H_7NO_2S$: C, 53.04; H, 3.59; N, 7.73. Found: C, 53.10; H, 3.90; N, 7.76.

3-Methyl-6-oxiranylmethoxy-2(3*H*)-benzoxazolone (**24**).

To a solution of **22** (16.5 g, 100 mmol) in acetonitrile (200 ml) was added anhydrous potassium carbonate (43.8 g, 300 mmol) and epibromhydrin (19.4 ml, 200 mmol). The reaction mixture was stirred at reflux for 48 hours, filtered, evaporated *in vacuo*. The residue was purified by column chromatography (silica gel-chloroform). The fractions containing the desired material were evaporated *in vacuo*, and the residue was triturated in petroleum ether to give pure **24** in 81% yield: mp 117-119 °C; ir (potassium bromide): ν 1765 (2(3*H*)-benzoxazolone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.75 and 2.90 (two dd, each 1H, CH of CH_2 of oxirane, Jgem = 5.1 Hz, Jvic1 = 2.65 Hz, Jvic2 = 4.70 Hz), 3.35 (m, 4H, CH of oxirane and NCH_3), 3.90 and 4.27 (two dd, each 1H, CH of CH_2, Jgem = 11.40 Hz, Jvic1 = 6.80 Hz, Jvic2 = 2.70), 6.60-9.95 (m, 3H, H_4, H_5, H_7).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.90; H, 5.12; N, 6.40.

3-Methyl-6-oxiranylmethoxy-2(3*H*)-benzothiazolone (**25**).

The reaction was carried out as described for compound **24**. Recrystallization from ethanol gave **25** in 80% yield: mp 82-83 °C; ir (potassium bromide): ν 1650 (2(3*H*)-benzothiazolone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.71 and 2.85 (two dd, each 1H, CH of CH_2 of oxirane, Jgem = 5.0 Hz, Jvic1 = 2.70 Hz, Jvic2 = 4.80 Hz), 3.34 (m, 4H, CH of oxirane and NCH_3), 3.83 and 4.33 (two dd, each 1H, CH of CH_2, Jgem = 11.50 Hz, Jvic1 = 6.50 Hz, Jvic2 = 2.60), 7.00 (dd, 1H, H_5, J*ortho* = 8.80 Hz, J*meta* = 2.50 Hz), 7.22 (d, 1H, H_4, J*ortho* = 8.80 Hz), 7.35 (d, 1H, H_7, J*meta* = 2.50 Hz),.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.70; H, 4.64; N, 5.90. Found: C, 55.72; H, 4.78; N, 5.88.

(4-{2-[(2-Hydroxy-3-(3-methyl-2(3*H*)-benzoxazolon-6-yl)-oxypropyl)amino] ethyl}phenoxy)acetic Acid Ethyl Hydrochloride (**26**).

A mixture of compound **10** (2.6 g, 10 mmol), and triethylamine (1.4 ml, 10 mmol) in dimethylsulfoxide was heated at 50 °C. After 10 minutes compound **24** (2.21 g, 10 mmol) was added and the reaction mixture was heated for 11 hours at 50 °C. The solution was quenched with cold water and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulfate and evaporated *in vacuo* to give a residue which was triturated with diethylether saturated with gaseous hydrochloric acid. The precipitate was collected, dried and recrystallized from methanol to give **26** in 42% yield: mp 201-204 °C; ν 3380 (OH), 1750 (2(3*H*)-benzoxazolone and ester CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.20 (t, 3H, CH_2CH_3, J = 7.00 Hz), 3.00-3.20 (m, 6H, $CH_2CH_2NHCH_2$), 3.30 (s, 3H, NCH_3), 3.70 (m, 1H, CHOH), 3.95 (d, 2H, $CHCH_2O$, J = 5.20 Hz), 4.15 (q, 2H, CH_2CH_3, J = 7.00 Hz), 4.75 (s, 2H, $COCH_2$), 5.95 (br s, 1H, OH exchangeable with D_2O), 6.83-6.90 (m, 3H, H_4, $H_{2'}$, $H_{6'}$), 7.10 (d, 1H, H_7, J*ortho* = 2.45 Hz), 7.16-7.18 (m, 3H, H_5, $H_{3'}$, $H_{5'}$), 8.90 (br s, 1H, NH of NH_2^+ exchangeable with D_2O), 9.20 (br s, 1H, NH of NH_2^+ exchangeable with D_2O).

Anal. Calcd. for $C_{23}H_{28}N_2O_7$•HCl: C, 57.44; H, 6.08; N, 5.82. Found: C, 57.54; H, 6.03; N, 6.03.

(4-{2-[(2-Hydroxy-3-(3-methyl-2(3*H*)-benzothiazolon-6-yl)-oxypropyl)amino]ethyl}phenoxy)acetic Acid Ethyl Hydrochloride (**27**).

The reaction was carried out as described for compound **26**. Recrystallization from ethanol gave **27** in 51% yield: mp 148-151 °C; ir (potassium bromide): ν 3380 (OH), 1720 (ester), 1670 (2(3*H*)-benzothiazolone CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.21 (t, 3H, CH_2CH_3, J = 7.10 Hz), 2.80-2.60 (m, 6H, $CH_2CH_2NHCH_2$), 3.30 (s, 3H, NCH_3), 4.16 (q, 2H, CH_2CH_3, J = 7.10 Hz), 4.38 (m, 3H, CH(OH)CH_2O), 4.70 (s, 2H, $COCH_2$), 5.00 (br s, 1H, OH exchangeable with D_2O), 6.82 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.50 Hz), 6.97 (dd, 1H, H_5, J*ortho* = 8.80 Hz, J*meta* = 2.50 Hz), 7.12 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.50 Hz), 7.21 (d, 1H, H_4, J*ortho* = 8.80 Hz), 7.31 (d, 1H, H_7, J*meta* = 2.50 Hz), 8.90 (br s, 1H, NH of NH_2^+ exchangeable with D_2O), 9.30 (br s, 1H, NH of NH_2^+ exchangeable with D_2O).

Anal. Calcd. for $C_{23}H_{28}N_2O_6S$•HCl: C, 55.58; H, 5.88; N, 5.64. Found: C, 55.83; H, 6.10; N, 5.67.

(4-{2-[(2-Hydroxy-3-(3-methyl-2(3*H*)-benzoxazolon-6-yl)oxypropyl)amino]ethyl}phenoxy)acetic Acid Hydrochloride (**6**).

Compound **26** (0.48 g, 1 mmol) was dissolved in 6 *M* hydrochloric acid (80 ml). The solution was heated under reflux for 5 minutes, and then cooled to 4 °C to obtain a precipitate that was isolated by filtration and recrystallized from ethanol-water (7/3) to give **6** in 76% yield: mp 230-233 °C; ir (potassium bromide): ν 3460 (OH), 1750 (2(3*H*)-benzoxazolone CO), 1715 (carboxylic CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.90-3.20 (m, 6H, $CH_2CH_2NHCH_2$), 3.35 (s, 3H, NCH_3), 4.00 (d, 2H, $CHCH_2O$, J = 5.10 Hz), 4.20 (m, 1H, CHOH), 4.65 (s, 2H, $COCH_2$), 6.00 (br s, 1H, OH exchangeable with D_2O), 6.63-7.19 (m, 7H, $H_{aromatics}$), 8.76 (br s, 1H, NH of NH_2^+ exchangeable with D_2O), 8.90 (br s, 1H, NH of NH_2^+ exchangeable with D_2O), 13.00 (br s, 1H, COOH exchangeable with D_2O).

Anal. Calcd. for $C_{21}H_{24}N_2O_7$•HCl: C, 55.69; H, 5.57; N, 6.19. Found: C, 55.34; H, 5.57; N, 6.12.

(4-{2-[(2-Hydroxy-3-(3-methyl-2(3*H*)-benzothiazolon-6-yl)-oxypropyl)amino]ethyl}phenoxy)acetic Acid Hydrochloride (**7**).

The reaction was carried out as described for compound **6**. Recrystallization from acetonitrile gave **7** in 76% yield: mp 187-190 °C; ir (potassium bromide): ν 3360 (OH), 1715 (2(3*H*)-benzothiazolone and carboxylic CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.90-3.30 (m, 6H, C*H*$_2$C*H*$_2$NHC*H*$_2$), 3.35 (s, 3H, NCH_3), 4.00 (d, 2H, CHC*H*$_2$O, J = 4.70 Hz), 4.25 (m, 1H, C*H*OH), 4.65 (s, 2H, $COCH_2$), 6.00 (br s, 1H, OH exchangeable with D_2O), 6.87 (d, 2H, $H_{2'}$, $H_{6'}$, J*ortho* = 8.50 Hz), 7.00 (dd, 1H, H_5, J*ortho* = 8.80 Hz, J*meta* = 2.20 Hz), 7.18 (d, 2H, $H_{3'}$, $H_{5'}$, J*ortho* = 8.50 Hz), 7.25 (d, 1H, H_4, J*ortho* = 8.80 Hz), 7.37 (d, 1H, H_7, J*meta* = 2.20 Hz), 8.90 (br s, 1H, NH of NH_2^+ exchangeable with D_2O), 9.14 (br s, 1H, NH of NH_2^+ exchangeable with D_2O), 13.00 (br s, 1H, COOH exchangeable with D_2O).

Anal. Calcd. for $C_{21}H_{24}N_2O_6S$•0.5H_2O•HCl: C, 52.88; H, 5.30; N, 6.21. Found: C, 52.76; H, 5.49; N, 5.86.

Acknowledgment.

We thank the Laboratoire d'Application de Résonance Magnétique Nucléaire (LARMN) of the Université de Lille 2 and particularly Dr Christophe Bochu for his aid with the interpretation of the nmr spectra.

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[*] E-mail: syous@phare.univ-lille2.fr.

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