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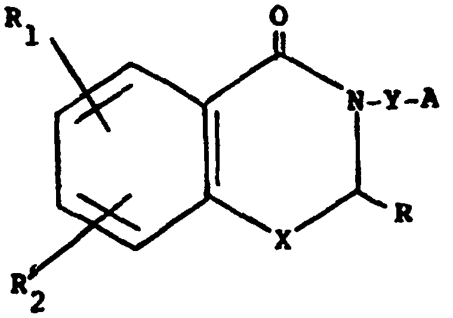
**(54) Title:** BENZOXAZINONES AND BENZOTHIAZINONES ENDOWED WITH THERAPEUTIC ACTIVITY

**(57) Abstract**

Compounds of general formula (I) wherein X is an oxygen or sulfur atom; Y is alkylene or cycloalkylene; A is hydroxy, alkoxy, acyloxy, mercapto, alkyl-sulfonyloxy, phenyl-sulfonyloxy, (a) or (b) wherein $R_3$ is an alkyl or alkylene group ω-substituted by 2,3-dihydro-4H-1,3-benzoxazin-4-one-N-yl; R is hydrogen, alkyl or phenyl; $R_1$ and $R_2$ are independently hydrogen, halogen, alkoxy, trifluoromethyl or alkyl; and the pharmaceutically acceptable acid and base salts thereof, are useful as therapeutically active substances.



(I)

$-O\overset{O}{\overset{\|}{S}}-O-R_3$

(a)

$-O\overset{O}{\overset{\|}{C}}OR_3$

(b)

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# BENZOXAZINONES AND BENZOTHIAZINONES ENDOWED WITH THERAPEUTIC ACTIVITY

The present invention relates to the therapeutic use of 2,3-dihydro-4H-1,3-benzoxazin- and -benzothiazin-4-ones.

2,3-Dihydro-4H-1,3-benzoxazin-4-ones unsubstituted on the nitrogen atom were described by B.W. Horrom et al., J. Org. Chem., 72, 721 (1950) as endowed with analgesic activity. Other 2,3-dihydro-4H-1,3-benzoxazin-4-ones were disclosed by R.B. Gammil, J. Org. Chem., 46, 3340 (1981).

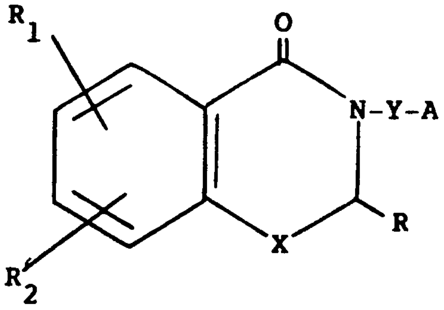
N-substituted derivatives of said heterocycle were described by J. Finkelstein et al., J. Med. Chem., 11, 1038 (1968) as antinflammatory agents. Also, 6-amino derivatives showing antinflammatory activity were disclosed by F. Fontanini et al., Riv. Farmacol. Ter., 4(1), 119 (1973) (Chem. Abs. 73745n, Vol. 79, page. 40, 1073).

The publication of the patent application EP-A-0 490 183 (in the name of the applicant) shows 2,3-dihydro-4H-1,3-benzoxazin- and -benzothiazin-4-ones having a $-ONO_2$ group: these compounds are endowed with a good cardiovascular activity, particularly against angina.

The publication of the patent application EP-A-0 359 627 describes benzoxazin-4-ones useful as agents inducing bradycardia, anti-ischemiscs and calcium-antagonists.

It has been now surprisingly found that 2,3-dihydro-4H-1,3-benzoxazin- and -benzothiazin-4-ones, some of them being already known as intermediates for the synthesis of compounds claimed in patent applications EP-A-0 490 183 and EP-A-0 359 627, are therapeutically active, particularly in the cardiovascular field.

Therefore, the present invention relates to compounds of the general formula (I)



(I)

wherein X is an oxygen or a sulphur atom;

Y represents methylene, ethylene, $(C_{3-6})$alkylene optionally branched, or cyclopentylene, cyclohexylene or cycloheptylene optionally substituted with $(C_{1-4})$alkyl;

A is hydroxy; $(C_{1-6})$alkoxy, formyloxy; $(C_{2-6})$acyloxy; mercapto; $(C_{1-6})$alkyl-mercapto; mesyloxy; $(C_{2-6})$alkyl-sulfonyloxy; tosyloxy; phenyl-sulfonyloxy optionally substituted with $(C_{2-6})$alkyl; $-O\overset{\overset{O}{\|}}{S}-O-R_3$ or $-O\overset{\overset{O}{\|}}{C}OR_3$ wherein $R_3$ is a $(C_{1-6})$alkyl group, methylene, ethylene or $(C_{3-6})$alkylene $\omega$-substituted with a 2,3-dihydro-4H-1,3-benzoxazin-4-one-N-yl residue;

R represents hydrogen, $(C_{1-6})$alkyl or phenyl;

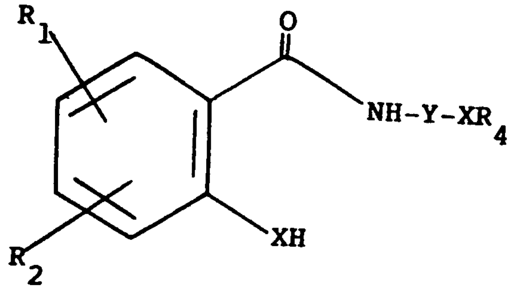
$R_1$ and $R_2$ are independently hydrogen, halogen, $(C_{1-6})$alkoxy, trifluoromethyl, and $(C_{1-6})$alkyl;

and the pharmaceutically acceptable acid or base salts thereof, useful as therapeutically active substances.

Specifically, the invention relates to the use of the compounds of formula (I) as agents useful in the cardiovascular field.

As intended hereinbelow, the alkyl groups essentially identify methyl, ethyl, propyl, i-propyl, butyl, 2-methyl-propyl, n-pentyl, 3-methylbutyl, i-pentyl, n-hexyl and the like, while the alkoxy groups are preferably selected from the group consisting of methoxy, ethoxy, propoxy, i-propoxy, butoxy, 2-methylbutoxy and t-butoxy. As linear or branched $(C_{3-6})$alkylene group it is intended, e.g., 2-methylethylene, 1,3-propylene, 1,4-butylene, 2-ethylethylene, 3-methylpropylene, 1,5-pentylene, 2-ethylpropylene, 2-methylbutylene, 1,6-hexylene, 1-ethyl-1-methylpropylene, 3-methylpentylene and the like. As $(C_{2-6})$acyloxy it is intended, e.g., acetyloxy, propionyloxy, butyryloxy, hexanoyloxy, oxalyloxy, malonyloxy, succinyloxy.

The compounds of the present invention are prepared according to procedures known to the skilled in the art. For example, the compounds of formula (I) wherein X, Y, R, $R_1$ and $R_2$ are as defined above, A is hydroxy, $(C_{1-6})$alkoxy, formyloxy or $(C_{2-6})$acyloxy, may be obtained according to what taught by the publication of the Patent application EP-A-0 490 183, by reacting a salicylamide or thiosalicylamide of formula (II)



(II)

wherein $R_1$, $R_2$, X and Y are as defined above, and $R_4$ is hydrogen, $(C_{1-6})$alkyl or $(C_{1-6})$acyl, with an aldehyde of formula (III)

R-CHO (III)

wherein R is as above, or a derivative or a precursor thereof. The condensation generally occurs in an acidic environment, for example in a system constituted by a strong mineral acid and acetic acid, thereby obtaining compounds of formula (I) wherein $R_4$ is acetyl, or by molecular sieves in the presence of sulfonic acids such as p-toluenesulfonic acid, methanesulfonic acid, α and ß-naphthalenesulfonic acids, phosphoric acids, esters and analogues thereof. The condensation is carried out in the presence of an organic solvent, preferably an inert organic solvent such as ethyl acetate, acetonitrile, benzene, nitrobenzene or chlorobenzene, halogenated aliphatic hydrocarbons such as methylene chloride, chloroform, 1,2-dichloroethane or 1,1,2-trichloroethylene, cyclohexane, tetrahydrofuran, tetrahydropyran, dimethylformamide, dimethylacetamide. The reaction temperature may vary within quite wide limits without prejudice for the course of the reaction. The preferred range of temperature is comprised between about -10°C and the reflux temperature of the reaction mixture, and the reaction is completed in a period of time ranging between about 2 and about 30 hours.

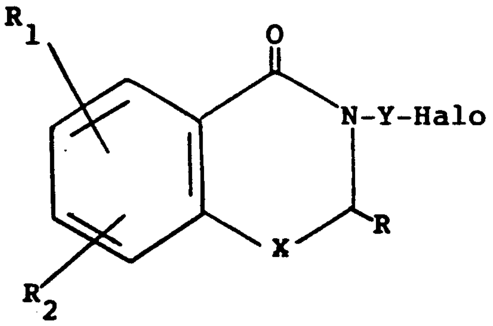
The molar quantities of the reagents of formula (II) and (III) are not critical for the good course of the cyclization, and such reagents may be used in the widest stoichiometric ratios. When compounds of formula (I) wherein R is hydrogen or methyl are desired, precursors of the compound of formula (III) such as paraformaldehyde and the paraldehyde are preferably employed.

Compounds of formula (I) wherein X, Y, R, $R_1$ and $R_2$ are as above, and A is hydroxy, may be used as reagents for preparing other compounds of formula (I).

For example, when compounds of (I) wherein X, Y, R, $R_1$ and $R_2$ are as above, and A represents formyloxy, $(C_{2-6})$acyloxy, mesyloxy, $(C_{2-6})$alkylsulfonyloxy, tosyloxy, phenyl-sulfonyloxy optionally substituted with $(C_{2-6})$alkyl, $-O\overset{\overset{O}{\|}}{S}-O-R_3$ or $-O\overset{\overset{O}{\|}}{C}OR_3$ wherein $R_3$ is a $(C_{1-6})$alkyl group, methylene, ethylene or $(C_{3-6})$alkylene $\omega$-substituted by a 2,3-dihydro-4H-1,3-benzoxazin-4-one-N-yl residue are desired, a compound of formula (I) wherein A is hydroxy is treated with a suitable carboxylic or sulfonic acid activated in form of anhydride, halide or imidazolide, used in excess, preferably in the presence of an organic base such as pyridine. Suitable solvents for such synthesis are, e.g., chloroform or methylene chloride, while the reaction temperature ranges between about -10°C and the room temperature, and the reaction time is of about 1-20 hours. In the case of

$-O\overset{O}{\overset{\|}{S}}-O-R_3$ or $-O\overset{O}{\overset{\|}{C}}OR_3$, at the end of the reaction a suitable amount of the $R_3OH$ desired alcohol is added.

Also, the compounds of formula (I) wherein A is hydroxy may yield compounds of formula (I) wherein A is mercapto or $(C_{1-6})$alkyl-mercapto, by an intermediate of formula (IV)



(IV)

wherein X, Y, R, $R_1$ and $R_2$ are as above, and Halo is an halogen atom, preferably chlorine. Such intermediate is obtained by treating the OH group with halogenating agents such as, e.g., thionyl chloride, sulfuryl chloride, phosphorous trichloride, phosphorous pentachloride, phosphorous oxytrichloride, phosphorous tribromide, sulfuryl bromide and the like. Said halogenation reaction occurs in an organic solvent, preferably in an inert organic solvent selected from the ones employed for the synthesis of the compound of formula (I) described above, at a temperature ranging between the room temperature and the reflux temperature of the reaction mixture. The compound of formula (IV) is converted into a compound of formula (I) wherein A is mercapto, by reaction with thiourea in alcoholic solution, at the reflux temperature of the reaction mixture, for about 5-12 hours, and subsequent hydrolysis with strong organic bases such as an alkali metal hydroxide, at the reflux temperature for about 2-10 hours. Subsequently, the compound of formula (I) wherein A is mercapto may be converted into a compound of formula (I) wherein A is $(C_{1-6})$alkyl-mercapto, by treatment with the suitable acyl halide in the presence of an organic base such as diazabicycloundecene, according to what taught by Patai, 2nd part, pages 721-735.

The compounds of formula (I) wherein A is hydroxy may also provide compounds of formula (I) wherein A is $(C_{1-6})$alkoxy, according to the so-called Williamson's reaction carried out with the suitable acyl halide.

In general, compounds of formula (I) may be converted into other compounds of formula (I) by means of suitable procedures for modifying the substituents $R_1$ and $R_2$, wholly familiar to the skilled in the art. In any case, the conversion of an $R_1$ or $R_2$ group into another $R_1$ or $R_2$ group having a meaning comprised by formula (I) may occur following conventional procedures familiar to the skilled in the art. These procedures are in the scope of the invention together with the obvious modifications of the just disclosed methods for preparing the compounds of the invention.

Hereinbelow preparation examples for some of the compounds of the invention are provided. Unless otherwise indicated the $^1H$-NMR spectra were carried out in dimethylsulfoxide (DMSO).

**EXAMPLE 1**

2,3-Dihydro-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)salicylamide was prepared as described in Aust. J. Chem., 25, 1797 (1972).

B) 5.5 g (0.03 mole) of the compound under A) and 0.57 g (0.003 mole) of p-toluenesulfonic acid were dissolved in 100 ml of benzene, and 2.7 g of paraformaldehyde were added to the resulting mixture. The reaction mixture was heated to 90°C for 3 hours, distilling off the formed water and, after cooling to room temperature, washed with water. The organic phase was recovered and, after evaporation of the solvent, there were obtained 4.7 g of a residue which was dissolved in 150 ml of tetrahydrofuran and 14 ml of 1N HCl. The mixture was refluxed for 8 hours, cooled to room temperature and extracted with ethyl acetate. The organic phase was dried and evaporated under vacuum, thus yielding 3.76 g of the title product.

m.p. 59-61°C (methylene chloride/acetone 1:9 v/v).

$^1$H-NMR (200 MHz): 7.82 (1H, dd); 7.54 (1H, dt); 7.18 (1H, t); 7.07 (1H, d); 5.34 (2H, s); 3.57 (4H, s).

## EXAMPLE 2

### 3-(2'-Acetoxyethyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one

A solution of 10 g (0.05 mole) of the compound of Example 1 in 200 ml of chloroform and 4.18 ml (0.05 mole) of pyridine was added with 19.6 ml (0.207 mole) of acetic anhydride. The solution was left at room temperature for 12 hours, then washed with water, and the organic phase was dried over sodium sulfate and evaporated to dryness. The crude obtained was purified by flash chromatography (eluent: hexane/ethyl acetate 6:4), thus yielding 2.4 g of the title product.

m.p. 67°C (ethyl acetate/hexane).

$^1$H-NMR (200 MHz): 7.82 (1H, dd); 7.55 (1H, dt); 7.15

(2H, m); 5.35 (2H, s); 4.17 (2H, t); 3.79 (2H, t); 2.00 (3H, s).

**EXAMPLE 3**

3-(2'-Acetoxyethyl)-2,3-dihydro-6-methyl-4H-1,3-benzoxazin-4-one

A) 8.5 g of methyl 5-methyl-salicylate (J. Chem. Soc., 661, 1961) in 3.7 ml of 2-aminoethanol were heated to 170°C for 3 hours. After cooling to room temperature the reaction mixture was taken up in ethyl acetate, washed with 5% hydrochloric acid and dried over anhydrous sodium sulfate. There were obtained 9 g of N-(2'-hydroxyethyl)-5-methyl-salicylamide.

m.p. 73-75°C (hexane).

B) A solution of 8 g (0.041 mole) of the compound under A) in 500 ml of chloroform and 11 ml of glacial acetic acid was added with 4 g of paraformaldehyde. The mixture was cooled to 0°C and added with 10 g of gaseous hydrochloric acid in 30 minutes, then the resulting solution was stirred at room temperature for 24 hours. The oily layer was eliminated and the chloroform phase was washed with water and dried over sodium sulfate. After evaporating the solvent, the resulting crude was purified on a silica gel column by eluting with methylene chloride/acetone (85:15 v/v) thus yielding 6 g of the title product.

m.p. 53-55°C (hexane).

$^1$H-NMR (80 MHz): 7.61 (1H, d); 7.30 (1H, dd); 6.92 (1H, d); 5.30 (2H, s); 4.15 (2H, t); 3.71 (2H, t); 2.02 (3H, s).

**EXAMPLE 4**

2,3-Dihydro-3-(2'-hydroxyethyl)-6-methyl-4H-1,3-benzoxazin-4-one

A solution of 6 g (0.024 mole) of the compound of Example 3, in 120 ml of methanol was added with 1.4 g (0.013 mole) of sodium carbonate, and the resulting mixture was left at room temperature for 12 hours. After evaporating the solvent, the resulting crude was taken up in methylene chloride, and the resulting organic phase was washed with water and dried over sodium sulfate. After evaporating methylene chloride, there were obtained 4.2 g of the title product.

m.p. 59-61°C (diethyl ether)

$^1$H-NMR (80 MHz): 7.60 (1H, d); 7.30 (1H, dd); 6.90 (1H, d); 5.30 (2H, s); 4.83 (1H, t); 3.56 (4H, m); 2.30 (3H, s).

**EXAMPLE 5**

3-(2'-Acetoxyethyl)-7-chloro-2,3-dihydro-4H-1,3-benzoxazin-4-one

A) 4-Chloro-N-(2'-hydroxyethyl)-salicylamide was prepared following the procedure of Example 3,A) starting from 20 g of methyl 4-chlorosalicylate (Chem. Abs. 81, 3624q) and 8 ml of 2-aminoethanol. Yield: 11 g m.p. 95-97°C (chloroform).

B) From 11 g (0.051 mole) of the compound under A) and 4.5 g of paraformaldehyde, following the procedure of Example 3,B), there were obtained 9 g of the title product.

m.p. 92-94°C (hexane).

$^1$H-NMR (80 MHz): 7.82 (1H, d); 7.30÷7.08 (2H, m); 5.35 (2H, s); 4.15 (2H, t); 3.70 (2H, t); 2.00 (3H, s).

**EXAMPLE 6**

7-Chloro-2,3-dihydro-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

From 8 g (0.03 mole) of the compound of Example 5 and following the procedure of Example 4, there were obtained 6.1 g of the title product.

m.p. 104-106°C (hexane).

$^1$H-NMR (80 MHz): 7.83 (1H, d); 7.30÷7.10 (2H, m); 5.36 (2H, s); 4.86 (1H, t); 3.60 (4H, m).

**EXAMPLE 7**

3-(2'-Acetoxyethyl)-2,3-dihydro-7-methyl-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-4-methylsalicylamide was prepared according to the procedure of Example 3,A) starting from 20 g of methyl 4-methylsalicylate (Chem. Abs. 64, 6568d) and 9 ml of 2-aminoethanol. Yield: 16.7 g m.p. 78-80°C (hexane).

B) From 16 g (0.081 mole) of the compound under A) and 4.5 g of paraformaldehyde, and following the procedure of Example 3,B), there were obtained 13 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.59 (1H, d); 6.98 (1H, d); 6.91 (1H, s); 5.19 (2H, s); 4.18 (2H, t); 3.68 (2H, t); 2.01 (3H, s).

**EXAMPLE 8**

2,3-Dihydro-3-(2'-hydroxyethyl)-7-methyl-4H-1,3-benzoxazin-4-one

From 12 g of the compound of Example 7 and following the procedure of Example 4, there were obtained 9 g of the title product as an oil.

$^1$H-NMR (80 MHz): 7.73 (1H, d); 6.96÷6.63 (2H, m); 5.20 (2H, s); 3.96÷3.56 (4H, m); 2.36 (3H, s).

**EXAMPLE 9**

3-(2'-Acetoxyethyl)-2,3-dihydro-2-methyl-4H-1,3-benzoxazin-4-one

Starting from 18.4 g (0.101 mole) of the compound of Example 1,A) and 8.13 ml (0.061 mole) of paraldehyde, and following the procedure of Example 3,B), there were obtained 6.7 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.74 (1H, dd); 7.52 (1H, dt); 7.17 (1H, t); 7.02 (1H, d); 5.70 (1H, q); 4.22 (2H, t); 4.63÷3.83 (1H, m); 3.56÷3.23 (1H, m); 2.05 (3H, s); 1.56 (3H, d).

**EXAMPLE 10**

2,3-Dihydro-3-(2'-hydroxyethyl)-2-methyl-4H-1,3-benzoxazin-4-one

From 6 g (0.029 mole) of the compound of Example 9 and operating as described in Example 4, there were obtained 3.8 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.74 (1H, dd); 7.52 (1H, dt); 7.17 (1H, t); 7.01 (1H, d); 5.50 (1H, q); 3.90÷3.57 (4H, m); 1.52 (3H, d).

**EXAMPLE 11**

3-(2'-Acetoxyethyl)-2,3-dihydro-2,7-dimethyl-4H-1,3-benzoxazin-4-one

From 6 g (0.03 mole) of the compound of Example 7,A) and 2.4 ml (0.018 mole) of paraldehyde and operating as described in Example 3,B), there were obtained 2.5 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.63 (d, 1H); 6.92 (d, 1H); 6.88 (s, 1H); 5.66 (q, 1H); 4.28 (t, 2H); 4.08÷3.78 (m, 1H); 3.52÷3.22 (m, 1H); 2.35 (s, 3H); 2.02 (s, 3H); 1.52 (s, 3H)

### EXAMPLE 12

2,3-Dihydro-2,7-dimethyl-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

From 2.3 g (0.009 mole) of the compound of Example 11, following the procedure of Example 4, there were obtained 2.1 g of the title product as an oil.

$^1$H-NMR (80 MHz): 7.63 (1H,d); 7.00÷6.76 (2H,m); 5.66 (1H,q); 4.86 (1H, t); 3.70÷3.43 (4H, m); 2.36 (3H, s); 1.50 (3H, d).

### EXAMPLE 13

3-(2'-Acetoxyethyl)-6-chloro-2,3-dihydro-4H-1,3-benzoxazin-4-one

A) 5-Chloro-N-(2'-hydroxyethyl)-salicylamide was prepared following the procedure of Example 3,A) starting from 19 g of methyl 5-chlorosalicylate (Arch. Pharm. 296(10), 714, 1963) and 7.5 ml of 2-aminoethanol. Yield: 13.8 g

m.p. 100-102°C (hexane).

B) From 13 g (0.06 mole) of the compound under A) and 4.5 g of paraformaldehyde, following the method of Example 3,B), there were obtained 11 g of the title product.

m.p. 93-95°C (hexane).

$^1$H-NMR (80 MHz): 7.73 (1H, d); 7.53 (1H, dd); 7.10 (1H, d); 5.35 (2H, s); 4.16 (2H, t); 3.71 (2H, t); 2.02 (3H, s).

### EXAMPLE 14

6-Chloro-2,3-dihydro-3-(2'-hydroxyethyl)-4H-1,3-

benzoxazin-4-one

From 10 g (0.037 mole) of the compound of Example 13 and operating as described in Example 4, there were obtained 7 g of the title product.

m.p. 88-90°C (diethyl ether).

$^1$H-NMR (80 MHz): 7.73 (1H, d); 7.53 (1H, dd); 7.10 (1H, d); 5.36 (2H, s); 3.56 (4H, m).

**EXAMPLE 15**

N-(5'-Acetoxypentyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one

A) N-(5'-hydroxypentyl)salicylamide was prepared following the procedure of Example 3,A) starting from 17.6 g of methyl salicylate and 8.5 ml of 5-aminopentanol. Yield: 11 g. The compound was an oil used as such in the subsequent step.

B) From 11.4 g (0.051 mole) of the compound under A) and 4.5 g of paraformaldehyde and following the procedure of Example 3,B), there were obtained 9 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.79 (1H, dd); 7.51 (1H, dt); 7.14 (1H, t); 7.04 (1H, t); 5.29 (2H, s); 4.03 (2H, t); 3.44 (2H, t); 2.04 (3H, s); 1.60÷1.19 (6H, m).

**EXAMPLE 16**

2,3-Dihydro-3-(5'-hydroxypentyl)-4H-1,3-benzoxazin-4-one

From 8.5 g (0.031 mole) of the compound of Example 15 and operating as described in Example 4, there were obtained 5.3 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.79 (1H, dd); 7.51 (1H, dt); 7.14÷7.04 (2H, m); 5.29 (2H, s); 3.44 (4H, m); 1.60÷1.19 (6H, m).

**EXAMPLE 17**

2,3-Dihydro-3-(2'-hydroxyethyl)-7-methoxy-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-4-methoxy-salicylamide was prepared following the procedure described in Example 3,A), starting from 16.9 g of methyl 4-methoxysalicylate (J. Org. Chem., 23, 756, 1958) and 7 ml of 2-aminoethanol.

Yield: 9.5 g.

m.p. 92-94°C (hexane).

B) 9 g (0.042 mole) of the compound under A) and 0.81 g (0.004 mole) of p-toluenesulfonic acid were dissolved in 130 ml of benzene, and the resulting solution was added with a 4 Å molecular sieve and 1.55 g of paraformaldehyde. The mixture was refluxed for 2 hours and, after cooling to room temperature, added with 300 ml of ethyl acetate. The molecular sieve was filtered off, the solution was washed with water and the organic phase was recovered and dried over sodium sulfate. After evaporation of the solvent there were obtained 10.3 g of a residue which was purified by a silica gel column by eluting with ethyl acetate/hexane - 8:2 (v/v). Yield: 2.1 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.83 (1H, d); 6.63 (1H, dd); 6.42 (1H, d); 5.36 (2H, s); 4.88 (1H, t); 3.62÷3.47 (4H, m); 3.81 (3H, s).

**EXAMPLE 18**

2,3-Dihydro-N-(2-hydroxyethyl)-4H-1,3-benzothiazin-4-one

A) A solution of 5 g (0.03 mole) of methyl thiosalicylate (Synthesis, 59, 1974) in 4 ml (0.06 mole) of ethanolamine was heated to 140°C while distilling off the methanol. After 2 hours, the solution was poured into water and extracted with ethyl acetate. The organic phase was dried and evaporated under vacuum, thus yielding 4.2 g (0.01 mole) of bis-[2-(2-hydroxyethyl)carboxamidophenyl]disulfide which were dissolved as such in 32 ml of ethanol. The solution was heated to 65°C and dropwise added with 0.4 g (0.01 mole) of sodium borohydride in 21 ml of ethanol. The solution temperature was kept at 65°C for 1 hour, then brought to room temperature. The residue obtained by evaporation of the solvent was chromatographed on a silica gel column by eluting with ethyl acetate. There were obtained 1.4 g of N-(2-hydroxyethyl)-2-mercaptobenzamide as an oil which was used as such in the subsequent step.

B) A solution of 3.5 g (0.017 mole) of the compound under A) in 50 ml of dioxane was added with 1.59 g (0.053 mole) of paraformaldehyde. The solution was cooled to 0°C and saturated with gaseous hydrochloric acid, then brought to room temperature and stirred for 3 days. After dilution with water, the mixture was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated under vacuum, and the resulting residue was chromatographed through a silica gel column [eluent: ethyl acetate/hexane 8:2 (v/v)]. There were obtained 1.5 g of the title product as an oil.

$^1$H-NMR (80 MHz): 7.93÷7.80 (1H, m); 7.50÷7.13 (3H, m); 4.83 (2H, s); 3.63 (4H, m).

**EXAMPLE 19**

2,3-Dihydro-trans-3-(2'-hydroxycyclohexyl)-4H-1,3-benzoxazin-4-one

A) Trans-N-(2'-hydroxycyclohexyl)salicylamide was prepared following the procedure of Example 3,A) from 16 g of methyl salicylate and 12 g of trans-2-amino-cyclohexanol. Yield: 9.1 g

m.p.: 91-96°C (hexane).

B) The title product was prepared according to the procedure of Example 17,B), starting from 8.1 g (0.0319 mole) of the compound under A). Yield: 1.5 g.

m.p.: 87-89°C (hexane).

$^1$H-NMR (80 MHz): 7.90 (1H, dd); 7.33 (1H, dt); 7.03÷6.70 (2H, m); 3.56 (2H, m); 2.10÷1.15 (8H, m).

**EXAMPLE 20**

2,3-Dihydro-3-(1'-methyl-2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) N-(1'-methyl-2'-hydroxyethyl)salicylamide was prepared following the procedure of Example 3,A) starting from 18 g (0.118 mole) of salicylic acid methyl ester and 18.8 ml of 2-amino-1-propanol. Yield: 19 g. The compound was an oil which was used as such in the subsequent step.

B) Following the procedure of Example 1,B) and starting from 19 g (0.973 mole) of the compound under A), there were obtained 7.76 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.82 (1H, dd); 7.52 (1H, dt); 7.17 (1H, t); 7.05 (1H, d); 5.30 (2H, m); 4.50 (1H, m); 2.50 (2H, m); 1.20 (3H, d).

**EXAMPLE 21**

2,3-Dihydro-N-(2'-hydroxyethyl)-6-methoxy-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-5-methoxysalicylamide was prepared following the procedure of Example 3,A) starting from 25 g (0.137 mole) of 5-methoxy-salicylic acid methyl ester and 9.94 ml of 2-aminoethanol. Yield: 25 g. The compound was used as such in the subsequent step.

B) The title product was prepared as described in Example 1,B) starting from 20 g (0.094 mole) of the compound under A). Yield: 17.2 g as an oil.

$^1$H-NMR (80 MHz): 7.30÷6.90 (3H, m); 5.30 (2H, s); 3.80 (3H, s); 3.60 (4H, s).

**EXAMPLE 22**

2,3-Dihydro-N-(2'-hydroxyethyl)-7-trifluoromethyl-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-4-trifluoromethyl-salicylamide was prepared following the procedure of Example 3,A) starting from 26 g (0.118 mole) of 4-trifluoromethyl-salicylic acid methyl ester [J. Am. Chem. Soc., 76, 1051-4 (1954)] and 100 ml of 2-aminoethanol. Yield: 24 g. The compound obtained was used as such in the subsequent step.

B) The title product was prepared as described in Example 1,B) starting from 20 g (0.08 mole) of the compound under A). Yield: 13 g.

m.p.: 63-65 °C (hexane).

$^1$H-NMR (80 MHz): 7.92 (1H, d); 7.40 (1H, d); 7.36 (1H, s); 5.36 (2H, s); 3.53 (4H, s).

### EXAMPLE 23

### N-(2'-Acetoxyethyl)-2,3-dihydro-7-trifluoromethyl-4H-1,3-benzoxazin-4-one

Following the procedure of Example 2 and starting from 5.1 g (0.019 mole) of the compound of Example 22, there were obtained 4.7 g of the title product.

$^1$H-NMR (200 MHz): 8.00 (1H, d); 7.50 (1H, d); 7.48 (1H, s); 5.43 (2H, s); 4.17 (2H, t); 3.72 (2H, t); 2.00 (3H, s).

### EXAMPLE 24

### 2,3-Dihydro-3-(2'-hydroxyethyl)-8-methyl-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-3-methyl-salicylamide was prepared following the procedure of Example 3,A) starting from 24.2 g (0.145 mole) of 3-methyl-salicylic acid methyl ester and 100 ml of 2-aminoethanol. Yield: 28.9 g. The compound was used as such in the subsequent step.

B) The title product was prepared as described in Example 1,B) starting from 28.3 g (0.145 mole) of the compound under A). Yield: 15 g as an oil.

$^1$H-NMR (80 MHz): 7.59 (1H, d); 7.34 (1H, d); 7.00 (1H, t); 5.33 (2H, s); 3.58 (4H, m); 2.23 (3H, s).

### EXAMPLE 25

### 2,3-Dihydro-3-(2'-hydroxyethyl)-5-methyl-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-6-methyl-salicylamide was prepared following the procedure of Example 3,A) starting from 18.8 g (0.113 mole) of 6-methyl-salicylic acid methyl ester and 78 ml of 2-aminoethanol. Yield: 19.3 g.

m.p.: 134-135°C (hexane).

B) The title product was prepared as described in Example 1,B) starting from 13.6 g (0.069 mole) of the compound under A). Yield: 6.6 g as an oil.

$^1$H-NMR (80 MHz): 7.30 (1H, t); 6.86 (2H, m); 5.23 (2H, s); 3.56 (4H, m); 2.63 (3H, s).

**EXAMPLE 26**

2,3-Dihydro-N-(3'-hydroxypropyl)-4H-1,3-benzoxazin-4-one

A) N-(3'-hydroxypropyl)salicylamide was prepared following the procedure of Example 3,A) starting from 20 g (0.131 mole) of salicylic acid methyl ester and 13.2 ml of 3-aminopropanol. Yield: 24 g as an oil which was used as such in the subsequent step.

B) The title product was prepared as described in Example 1,B) starting from 17 g (0.087 mole) of the compound under A). There were obtained 7.75 g of the title product as an oil.

$^1$H-NMR (80 MHz): 7.76 (1H, dd); 7.50 (1H, dt); 7.10 (2H, m); 5.33 (2H, s); 3.52 (4H, m); 1.73 (2H, m).

**EXAMPLE 27**

2,3-Dihydro-N-(2'-hydroxy-1'-methyl-1'-propyl)-4H-1,3-benzoxazin-4-one

A) 31.24 g (0.146 mole) of salicylic acid methyl ester and 13 g (0.146 mole) of 3-amino-2-butanol was heated to 80°C for 4 hours then cooled to room temperature. The crude obtained was washed with hexane and purified by silica gel column chromatography [eluent: chloroform /acetone 10/1 v/v]. There were obtained 12 g of N-(1'-methyl-2'-hydroxy-1'-propyl)salicylamide as an oil which was used as such in the subsequent step.

B) The compound was prepared as described in Example 1,B) starting from 11 g (0.052 mole) of the compound under A). There were obtained 8.13 g of the title product as an oil.

$^1$H-NMR (80 MHz): 7.76 (1H, dd); 7.46 (1H, dt); 7.10 (2H, m); 5.33 (2H, s); 4.30 (1H, m); 3.76 (1H, m); 1.30 (6H, dd).

**EXAMPLE 28**

2,3-Dihydro-3-(2'-hydroxy-1'-propyl)-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxy-1'-propyl)salicylamide was prepared following the procedure of Example 3,A) starting from 18 g (0.118 mole) of salicylic acid methyl ester and 18.3 ml of 1-amino-2-propanol. Yield: 24 g as an oil which was used as such in the subsequent step.

B) The title product was prepared as described in Example 1,B) starting from 20 g (0.102 mole) of the compound under A). There were obtained 18 g as an oil.

$^1$H-NMR (200 MHz): 7.83 (1H, dd); 7.50 (1H, dt); 7.33÷7.00 (2H, m); 5.40 (2H, s); 4.00÷3.10 (3H, m); 1.10 (3H, d).

**EXAMPLE 29**

2,3-Dihydro-3-(2'-hydroxyethyl)-7-isopropoxy-4H-1,3-benzoxazin-4-one

A) N-(2'-hydroxyethyl)-4-isopropoxy-salicylamide was prepared following the procedure of Example 3,A) starting from 25.3 g (0.166 mole) of 4-isopropoxy-salicylic acid methyl ester [obtained by treating 4-isopropoxy-salicylic acid prepared according to Synthesis 758-760 (1984), with methanol and sulfuric acid] and 100 ml of 2-aminoethanol. Yield: 22 g. The compound was used as such in the subsequent step.

B) The title product was prepared as described in Example 1,B) starting from 5 g (0.028 mole) of the compound under A). There were obtained 3.1 g as an oil.

$^1$H-NMR (200 MHz): 7.70 (1H, d); 6.69 (1H, dd); 6.58 (1H, d); 5.31 (2H, s); 4.88 (1H, bs); 4.71 (1H, m); 3.53 (4H, m); 1.29 (6H, d).

## EXAMPLE 30

### 2,3-Dihydro-3-(2'-mercaptoethyl)-4H-1,3-benzoxazin-4-one

A) A solution of 9 g (0.046 mole) of the compound of Example 1 in 70 ml of chloroform was added with 3.54 ml (0.048 mole) of methylene chloride. The solution was heated to 70°C for 3 hours, then brought again to room temperature, washed with a solution of 5% sodium hydrogen carbonate, then with water. The organic phase was dried over sodium sulfate and evaporated. There were obtained 9.3 g of 2,3-dihydro-3-(2'-chloroethyl)-4H-1,3-benzoxazin-4-one.

B) A solution of 15 g (0.071 mole) of the compound under A) in 500 ml of ethanol was added with 16.1 g (0.2 mole) of thiourea. The mixture was refluxed for 8 hours, then brought to room temperature, treated with 42 ml of 10% NaOH and refluxed again for 5 hours. The solution was evaporated to dryness, the crude was taken up in water and extracted with chloroform. The organic phase was dried over sodium sulfate and evaporated. The crude was purified by flash-chromatography (eluent: chloroform), and there were obtained 2.3 g of the title product.

m.p.: 44-46°C (chloroform)

$^1$H-NMR (200 MHz): 7.82 (1H, dd); 7.54 (1H, dt); 7.17 (1H, t); 7.07 (1H, d); 5.38 (2H, s); 3.63 (2H, t); 2.72 (2H, q); 2.46 (1H, t).

**EXAMPLE 31**

2,3-Dihydro-3-(2'-methoxyethyl)-4H-1,3-benzoxazin-4-one

A) A solution of 10 g of methyl salicylate in 15 ml of acetonitrile was added with 5.5 ml of 2-methoxyethylamine, and then refluxed for 24 hours. At the end of the heating, the solution was evaporated to dryness under vacuum, taken up in ethyl acetate and washed with 1N hydrochloric acid and then with water. The organic phase was dried over sodium sulfate and concentrated to small volume. The formed solid was filtered and dried under vacuum thus yielding 9 g of N-(2'-methoxyethyl)salicylamide.

B) Following the procedure of Example 1,B) and starting from 9 g (0.046 mole) of the compound under A), there were obtained 8.3 g of the title product.

$^1$H-NMR (200 MHz, DMSO) 7.82 (1H, dd); 7.55 (1H, dt);

7.17 (1H, t); 7.07 (1H, d); 5.32 (2H, s); 3.67 (2H, m); 3.51 (2H, m); 3.29 (3H, s).

**EXAMPLE 32**

2,3-Dihydro-3-(2'-tosyloxyethyl)-4H-1,3-benzoxazin-4-one

A solution of 3 g (0.015 mole) of the compound of Example 1 in 15 ml of chloroform was added with 3.7 ml (0.046 mole) of pyridine and 8.88 g (0.046 mole) of tosyl chloride. After 2 hours the reaction mixture was washed with 1N HCl. The organic phase was dried over sodium sulfate and evaporated, and the resulting crude was purified by flash-chromatography (eluent: methylene chloride/ethyl acetate 98:2) thus yielding 3.34 g of the title product.

m.p.: 122-124°C (methylene chloride)

$^1$H-NMR (200 MHz): 7.77÷7.71 (3H, m); 7.55 (1H, dt); 7.33 (2H, m); 7.17 (1H, t); 7.06 (1H, d); 5.20 (2H, s); 4.23 (2H, t); 3.72 (2H, t); 2.32 (3H, s).

**EXAMPLE 33**

2,3-Dihydro-3-(2'-mesyloxyethyl)-4H-1,3-benzoxazin-4-one

A solution of 5 g (0.026 mole) of the compound of Example 1, in 80 ml of chloroform and 5.8 ml (0.072 mole) of pyridine, cooled to 0°C, was added with 5.6 ml (0.072 mole) of mesyl chloride dissolved in 20 ml of chloroform. After 6 hours the solution was washed with 1N HCl, water, 5% sodium hydrogen carbonate and finally with water. The organic phase, dried over sodium sulfate, was evaporated under vacuum. There were obtained 2.7 g of the title product.

m.p.: 76-78°C (methylene chloride)

$^{1}$H-NMR (200 MHz): 7.83 (1H, dd); 7.55 (1H, dt); 7.18 (1H, t); 7.09 (1H, d); 5.36 (2H, d); 4.39 (2H, t); 3.83 (2H, d); 3.22 (3H, s).

### EXAMPLE 34

Methyl 2-(2',3'-Dihydro-4'-oxo-1',3'-benzoxazin-3'-yl)ethylsulfite

A solution of 10 g (0.05 mole) of the compound of Example 1 in 200 ml of chloroform, cooled to -15°C was added with 3.77 ml (0.051 mole) of methylene chloride. After 1 hour, 2.1 ml of methanol were added. The reaction mixture was brought to room temperature and, after 5 hours, was evaporated. The resulting crude was purified by flash chromatography (eluent: hexane/ethyl acetate 1:1). There were obtained 4 g of the title product as an oil.

$^{1}$H-NMR (200 MHz): 7.82 (1H, dd); 7.54 (1H, dt); 7.17 (1H, t); 7.07 (1H, d); 5.35 (2H, s); 4.14 (2H, m); 3.77 (2H, m); 3.59 (3H, s).

### EXAMPLE 35

Bis-2'-(2,3-dihydro-4-oxo-1,3-benzoxazin-3-yl)ethylcarbonate

A solution of 4 g (0.02 mole) of the compound of Example 1 in 200 ml of methylene chloride was added with 120 mg (0.002 mole) of sodium methylate and 1.92 g (0.012 mole) of carbonyldiimidazole. The solution was left at room temperature for 23 hours, then washed with water. The organic phase was dried over sodium sulfate and evaporated to dryness. The crude was purified by flash-chromatography (eluent: hexane/ethyl acetate 6:4) thus yielding 2.5 g of the title product.

m.p.: 74-75°C (hexane/ethyl acetate 1:1)

$^1$H-NMR (200 MHz): 7.82 (2H, dd); 7.54 (2H, dt); 7.18 (2H, t); 7.07 (2H, d); 5.30 (4H, s); 4.25 (4H, t); 3.70 (4H, t).

**EXAMPLE 36**

2,3-Dihydro-3-(2'-ethoxyethyl)-4H-1,3-benzoxazin-4-one

Operating as in Example 31, from 12 g of 2-ethoxyethylamine, there were obtained 1.4 g of the title product.

$^1$H-NMR (200 MHz): 7.83 (1H, dd); 7.52 (1H, dt); 7.15 (1H, t); 7.05 (1H, d); 5.32 (2H, s); 3.65 (2H, m); 3.54 (2H, m); 3.45 (2H, q); 1.10 (3H, t).

**EXAMPLE 37**

Isopropyl 2-(2',3'-dihydro-4'-oxo-1',3'-benzoxazin-3'-yl)ethylsulfite

The title product was prepared as described in Example 34 starting from 10 g (0.051 mole) of the compound of Example 1, 3.78 ml (0.051 mole) of thionyl chloride and 398 ml (5.17 moles) of isopropyl alcohol. There were obtained 1.2 g of the title product as an oil.

$^1$H-NMR (200 MHz): 7.82 (1H, dd); 7.55 (1H, dt); 7.17 (1H, t); 7.08 (1H, d); 5.35 (2H, s); 4.71 (1H, m); 4.13 (2H, m); 3.78 (2H, m); 1.24 (3H, d); 1.21 (3H, d).

**EXAMPLE 38**

6,8-Dichloro-2,3-dihydro-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) 3,5-Dichloro-N-(2'-hydroxyethyl)-salicylamide was prepared following the procedure of Example 3,A) starting from 20.9 g (0.094 mole) of methyl 3,5-dichloro-salicylate and 6.85 ml (0.113 mole) of 2-aminoethanol. Yield: 14 g.

m.p. 137-139°C (hexane)

B) From 14 g (0.055 mole) of the compound under A) and 3.07 g of paraformaldehyde, and operating as described in example 3,B), there were obtained 2.7 g of the title product.

m.p. 98-100°C (hexane)

$^1$H-NMR (200 MHz): 7.88 (1H, d); 7.72 (1H, d); 5.47 (2H, s); 4.91 (1H, t); 3.57 (4H, m).

**EXAMPLE 39**

2,3-Dihydro-4,5-dimethoxy-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) 4,5-Dimethoxy-N-(2'-hydroxyethyl)-salicylamide was prepared by reacting 23 g (0.108 mole) of 4,5-dimethoxy-salicylic acid methyl ester (obtained as described in Synthesis, 758, 1984) with 100 ml of 2-aminoethanol at 170°C for 3 hours. After cooling to room temperature, the mixture was taken up in ethyl acetate, washed with 5% aqueous hydrochloric acid and dried over sodium sulfate. Yield: 18 g. The compound was used as such in the subsequent step.

B) The title product was prepared according to the procedure described in Example 17,B), starting from 15 g (0.062 mole) of the compound under A). Yield: 13 g.

$^1$H-NMR (200 MHz): 7.21 (1H, s); 6.67 (1H, s); 5.27 (2H, s); 4.84 (1H, 7); 3.81 (3H, s); 3.76 (3H, s); 5.52 (4H, m).

**EXAMPLE 40**

2,3-Dihydro-6-fluoro-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) 5-Fluoro-N-(2'-hydroxyethyl)-salicylamide was prepared as described in Example 3 A), starting from 4.9 g (0.03 mole) of 5-fluoro-salicylic acid methyl ester and 2.08 ml (0.034 mole) of 2-aminoethanol. Yield: 5.29 g.

b) The title product was prepared according to the procedure described in Example 17 B), starting from 5.2 g (0.026 mole) of the compound under A) and 2.37 g of paraformaldehyde. Yield: 3.1 g.

m.p.- 128-130°C (hexane)

$^1$H-NMR (200 MHz): 7.52 (1H, dd); 7.42 (1H, dt); 7.15 (1H, dd); 5.32 (2H, s); 4.90 (1H, t); 3.57 (4H, m).

**EXAMPLE 41**

2,3-Dihydro-6-ethyl-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) 5-Ethyl-N-(2'-hydroxyethyl)-salicylamide was prepared as described in Example 3 A), starting from 26.8 g (0.148 mole) of 5-ethyl-salicylic acid methyl ester (prepared as described in Synthesis, 758, 1984) and 10.7 ml (0.178 mole) of 2-aminoethanol. Yield: 29.8 g.

B) The title product was prepared according to the procedure described in Example 17 B), starting from 25 g (0.119 mole) of the compound under A) and 10.7 g of paraformaldehyde. Yield: 11.9 g.

$^1$H-NMR (200 MHz): 7.62 (1H, d); 7.37 (1H, dd); 6.97 (1H, d); 5.32 (2H, s); 4.87 (1H, t); 3.57 (4H, m); 2.62 (2H, q); 1.20 (3H, t).

**EXAMPLE 42**

2,3-Dihydro-6,7-dimethyl-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) 4,5-Dimethyl-N-(2'-hydroxyethyl)-salicylamide was prepared as described in Example 3,A), starting from 33.6 g (0.186 mole) of 4,5-dimethyl-salicylic acid methyl ester (prepared as in Synthesis, 758, 1984) and 13.5 ml (0.223 mole) of 2-aminoethanol. Yield: 34.4 g.

B) The title product was prepared according to the procedure described in Example 17,B), starting from 30.5 g (0.146 mole) of the compound under A) and 13.14 g of paraformaldehyde. Yield: 17.7 g.

m.p.= 89-91°C (hexane)

$^1$H-NMR (200 MHz): 7.55 (1H, s); 6.85 (1H, s); 5.27 (2H, s); 4.87 (1H, t); 3.55 (4H, m); 2.25 (3H, s); 2.20 (3H, s).

## EXAMPLE 43

### 6-Bromo-2,3-dihydro-3-(2'-hydroxyethyl)-4H-1,3-benzoxazin-4-one

A) 5-Bromo-N-(2'-hydroxyethyl)-salicylamide was prepared as described in Example 3,A), starting from 5.2 g (0.022 mole) of 5-bromo-salicylic acid methyl ester and 1.63 ml (0.027 mole) of 2-aminoethanol. Yield: 5.53 g.

B) The title product was prepared according to the procedure described in Example 17,B), starting from 5.4 g (0.021 mole) of the compound under A) and 1.87 g of paraformaldehyde. Yield: 1.84 g.

m.p.= 78-81°C (hexane)

$^1$H-NMR (200 MHz): 7.87 (1H, d); 7.70 (1H, d); 7.07 (1H, d); 5.37 (2H, s); 4.90 (1H, t); 3.57 (4H, m).

As already said above, the compounds of the invention possess cardiovascular activity. In particular they showed a remarkable antianginal and antiischemic activity in the lab animal.

These favourable biological properties are, in general, accompanied with a negligible hypotensive effect. Thus the compounds of the invention can be considered as potential drugs with a specific antianginal activity.

The *in vivo* antianginal activity was determined on anaesthetized Sprague Dawley rats (average weight - 350-400 g), according to the method described by M. Leitold et al., Arzneim. Forsch. 36, 1454, 1986. The test was carried out by intravenously administering the animals with 1 U.I/kg, equal to 3 mg/kg of Arg-vasopressin which induce a coronary spasm reproducible and electrocardiographically detectable by an increase of the T-wave. The animals were then intravenously treated with four increasing doses of compounds representative of the invention to measure their $ED_{50}$, i.e. the dose yielding a 50% of inhibition of the increasing of the T-wave. The compounds of the invention showed to have $ED_{50}$ ranging between about 1 and about 300 µg/Kg. Specifically, the compounds of Examples 1, 2 and 34 showed an $ED_{50}$ of, respectively, 87, 215 and 10.5 µg/Kg. Also, some compounds were tested as above, but orally administered. For example, the compound of Example 1 showed an $ED_{50}$ of 0.23 mg/Kg.

The antianginal activity of the claimed compounds was also tested by the metacholine-induced angina test described by Sakai K. et al., Pharmacol. Met., 5, 325-336, 1981. The percentage of inhibition of the ST-wave increase induced by metacholine (0.8 µg/kg i.v.) was measured after intravenous administration of the compounds of the invention. The results are set forth in the following Table 1.

**TABLE 1**

| Example | % of Inhibition at 3 μg/kg | | |
|---|---|---|---|
| | 1 min. | 10 min. | 30 min. |
| 4 | | 60.0 | 45.0 |
| 6 | 57.1 | 51.0 | 28.6 |
| 8 | 31.1 | | |
| 14 | 71.4 | 54.7 | 73.8 |
| 17 | 45.1 | 39.2 | |
| 18 | | 37.2 | 28.0 |
| 21 | 25.0 | 38.6 | 34.1 |
| 22 | 29.3 | 22.0 | 34.1 |
| 30 | 30.2 | 48.8 | 37.2 |
| 31 | 30.0 | 20.4 | |
| 38 | 40.6 | | |
| 39 | 23.0 | 52.3 | |

Following the same method the $ED_{50}$ of the compound of Example 1 was determined to be 73.5 μg/kg.

The test above was repeated by orally administering 0.3 mg/kg of the claimed compounds. The results are set forth in the following Table 2.

**TABLE 2**

| Example | % of Inhibition | |
|---|---|---|
| | 30 minutes | 120 minutes |
| 4 | | 52.6 |
| 14 | 71.2 | 73.1 |
| 34 | 46.8 | 21.8 |
| 21 | | 28 |

The same test showed that the compounds of the invention have an $ED_{50}$ per os ranging between about 100 and about 0.01 mg/kg.

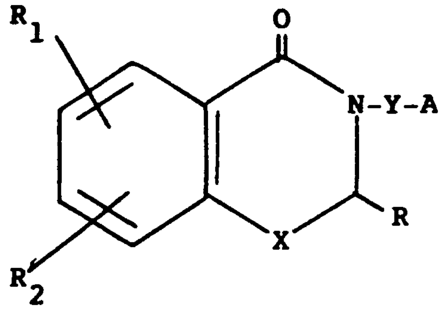
The favourable biological properties above are also accompanied by a low toxicity. The $LD_{50}$ values, calculated according to the method of Lichtfield and Wilcoxon, J. Pharm. Expt. Ther. 96, 99, 1949, are in fact higher than 500 mg/kg i.p. in mouse and 800 mg/kg p.o. in rat.

Object of the present invention is also the use of the claimed compounds as antianginal agents and agents useful in the treatment of ischemic cardiopathies, in connection with all the industrial aspects and applications of said use, comprising their incorporation into pharmaceutical compositions. Examples of these compositions are tablets, sugar-coated and film-coated tablets, syrups and phials, these latter being suitable for both the oral and the intramuscular or intravenous administration. They contain the active principle alone or in combination with common pharmaceutically acceptable carriers and excipients.

The dosages of active principle used in the antianginal therapy or to treat ischemic cardiopathies may vary within wide limits depending on the specific compound employed, and are chosen to provide the patient with an effective therapeutic protection for. For example, unit doses of from about 0.01 to about 1 mg may be administered from 1 to 4 times a day depending on the patient's necessity (prophylaxis, therapy, emergency).

## CLAIMS

1. Compounds of general formula (I)



(I)

wherein X is an oxygen or sulfur atom;
Y is methylene, ethylene, $(C_{3-6})$alkylene optionally branched, or cyclopentylene, cyclohexylene or cycloheptylene optionally substituted with $(C_{1-4})$alkyl;
A is hydroxy, $(C_{1-6})$alkoxy, formyloxy, $(C_{2-6})$acyloxy, mercapto, $(C_{1-6})$alkyl-mercapto, mesyloxy, $(C_{2-6})$alkylsulfonyloxy, tosyloxy, phenyl-sulfonyloxy optionally substituted with $(C_{2-6})$alkyl;
$-O\overset{\overset{O}{\|}}{S}-O-R_3$ or $-O\overset{\overset{O}{\|}}{C}OR_3$ wherein $R_3$ is a $(C_{1-6})$alkyl group, methylene, ethylene or $(C_{3-6})$alkylene ω-substituted by a 2,3-dihydro-4H-1,3-benzoxazin-4-one-N-yl residue;
R is hydrogen, $(C_{1-6})$alkyl or phenyl;
$R_1$ and $R_2$ are independently hydrogen, halogen, $(C_{1-6})$-alkoxy, trifluoromethyl, or $(C_{1-6})$alkyl;
and the pharmaceutically acceptable acid and base salts thereof, useful as therapeutically active substance.

2. Use of the compounds according to claim 1 for the preparation of a medicament useful in the cardiovascular field.

3. Use of the compounds according to claim 1 for the preparation of a medicament useful in the antianginal

therapy.

4. Pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutically inert excipient.

5. A substance useful in the cardiovascular therapy comprising a compound according to claim 1 together with a pharmaceutically inert excipient.

# INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/EP 94/02354

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D265/22 C07D279/08 A61K31/535 A61K31/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X | EP,A,0 490 183 (ITALFARMACO S.P.A.) 17 June 1992<br>cited in the application<br>see the whole document<br>--- | 1 |
| A | EP,A,0 527 081 (PIERRE FABRE MEDICAMENT) 10 February 1993<br>see claims<br>--- | 1-5 |
| A | GB,A,2 096 612 (FARMACEUTICI COLI SRL.) 20 October 1982<br>see the whole document<br>---<br>-/-- | 1,4 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "&" document member of the same patent family

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|---|---|
| Date of the actual completion of the international search<br>20 October 1994 | Date of mailing of the international search report<br>-8. 11. 94 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>Chouly, J |

# INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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