(12) UK Patent (19) GB (11) 2 231 330 (13) B

(54) Title of Invention

Thieno-triazolo-diazepine derivatives

(51) INT CL[5]; **C07D 495/22, A61K 31/55 // (C07D 495/22 211:00 243:06 249:08 307:64 333:00)**

(21) Application No
9010403.5

(22) Date of filing
09.05.1990

(30) Priority Data

(31) **8911030**

(32) **13.05.1989**

(33) **GB**

(43) Application published
14.11.1990

(45) Patent published
29.04.1992

(52) Domestic classification
(Edition K)
C2C CAA CQS CQT CQU
C145X C1470 C1510 C214
C215 C22Y C220 C25Y C253
C254 C256 C31Y C311 C313
C338 C351 C355 C36Y C364
C37Y C372 C373 C463 C464
C465 C553 C612 C613 C614
C625 C662 C675 C694 C697
C699 C771 C772 C80Y C802

(56) Documents cited
EP0176927 A2

(58) Field of search

As for published application
2231330 A *viz:*
UK CL(Edition K) **C2C CQS CQT CQU**
INT CL[4] **C07D**
ONLINE DATABASE: CAS ONLINE
updated as appropriate

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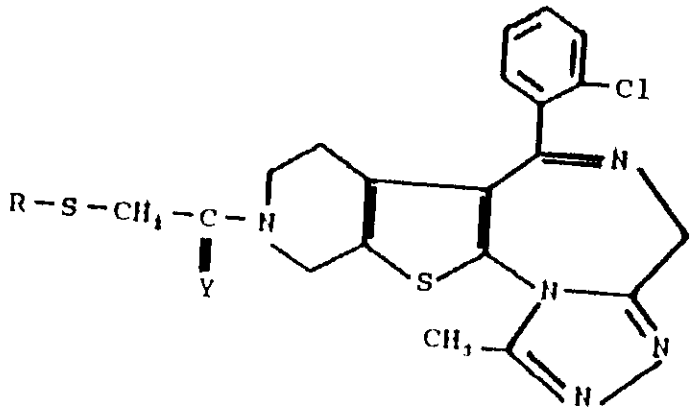
TITLE:

Thieno-triazolo-diazepine Derivatives

DESCRIPTION

The invention relates to derivatives of thieno-triazolo--diazepine, to a method for their preparation and to therapeutic compositions containing them. The thieno--triazolo-diazepine derivatives of the invention are of interest as anti-ischemic, anti-asthmatic and anti--allergic agents and as gastro-intestinal protectors. They are of particular interest in the treatment of ischemia.

The invention provides thieno-triazolo-diazepine derivatives of the general formula I

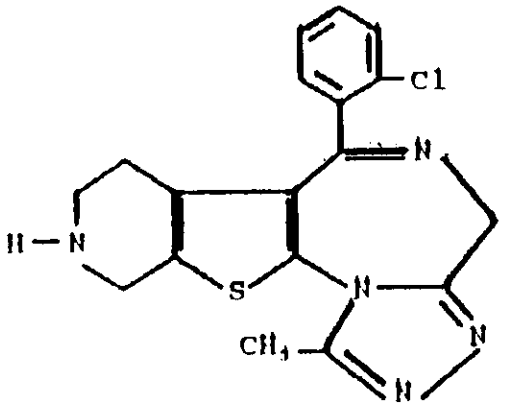


I

wherein Y represents an oxygen or sulphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms; a phenyl group; a phenyl group substituted by one or more of a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms, an alkoxy group having from 1 to 5 carbon atoms, a halogen atom, a trifluoromethyl group or an optionally substituted phenoxy group; or a furyl or thienyl group;

and further provides therapeutically acceptable salts of such derivatives.

The thieno-triazolo-diazepine derivatives of the general formula I wherein Y represents an oxygen atom may be prepared by treating the thieno-triazolo-diazepine compound of the formula II



II

with a compound of the general formula $RSCH_2COOH$ wherein R is as above defined, under nitrogen circulation, in the presence of a slight stoichiometric excess of hydroxybenzotriazole or dicyclohexylcarbodiimide, at about 0°C.

The thieno-triazolo-diazepine derivatives of the general formula I wherein Y represents a sulphur atom may be prepared by treating the corresponding thieno-triazolo--diazepine derivatives of the general formula I wherein Y represents an oxygen atom with Lawesson's reagent or with phosphorus pentasulphide in an aprotic solvent at a temperature of from room temperature to the reflux temperature of the reaction mixture.

These processes are within the scope of the invention.

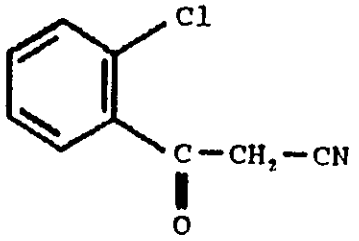
The invention further provides a therapeutic composition comprising a thieno-triazolo-diazepine derivative of the general formula I or a therapeutically acceptable salt thereof in admixture with a therapeutically acceptable diluent or carrier.

US patent No. 4621083 (and the equivalent European Patent No. 176927) disclose thieno-triazolo-diazepine derivatives having PAF-antagonistic activity. The compounds of this invention present a PAF-antagonistic

activity from ten to a thousand times greater than the diazepines disclosed in the abovementioned Patent, and also a more potent effectiveness.

The starting material of the general formula II may be prepared as described in the following preparative examples I to X.

I - (2-chloro)benzoylmethyl cyanide.

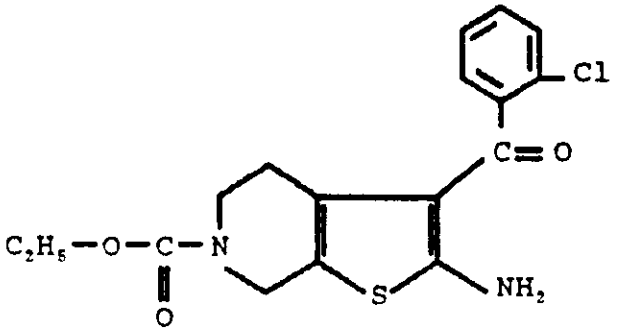


7 litres of anhydrous tetrahydrofuran (THF) and 115.9 g (1.36 mol) of previously dried cyanoacetic acid were poured into an appropriate reactor under nitrogen circulation at -70°C. 1715 ml (2.74 mol) of a 1.6 M solution of butyllithium in hexane was added dropwise, while allowing the temperature to rise from -70°C to 0°C. The reaction mixture was then stirred for one hour. Thereafter the reaction mixture was once more cooled to -70°C and a solution of 120 g (0.685 mol) of 2-chloro-benzoyl chloride in 1 litre of anhydrous THF was added dropwise.

After stirring for one hour at -70°C, the temperature was allowed to rise from -70°C to 0°C for one hour. Then there was added dropwise 3 litres of 1N hydrochloric acid. After stirring for a few minutes, the reaction mixture was extracted with chloroform. The organic phase was washed with a 10% aqueous sodium bicarbonate solution, then with a saturated sodium chloride solution, dried and filtered. The solvent was evaporated off to give 135 g of residue. Crystallization was effected by the addition of diisopropyl ether, and the product was

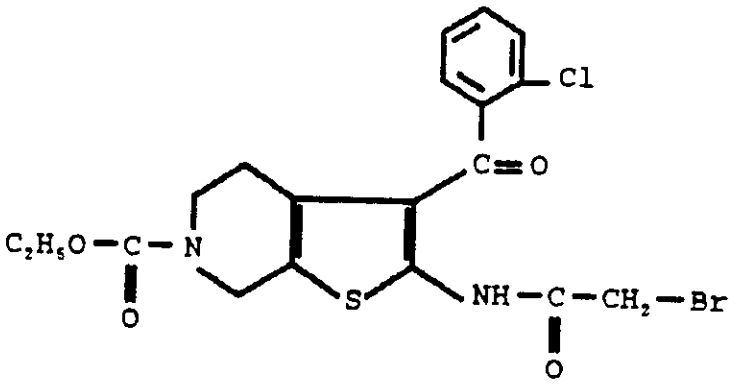
filtered off, and washed with hexane to give 97.2 g of the title compound (yield 79%).

II - 2-amino-3-(2-chlorobenzoyl)-6-ethoxycarbonyl-4,5,6,7 tetrahydro-pyrido [3,4-b] thiophene.



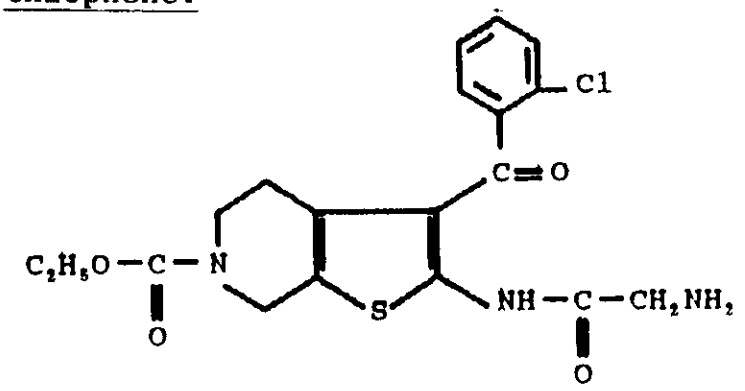
Into a two litre erlen flask fitted with a cooler, were poured 85.5 g (0.501 mol) of N-carbethoxy-4-piperidone, 90 g (0.501 mol) of (I), 19.3 g (0.600 mol) of flowers of sulphur and 44.4 g (0.501 mol) of morpholine, in 550 ml of methanol. The mixture was refluxed for one hour. After evaporation of 250 ml of solvent, the desired compound precipitated. It was filtered off, washed with ethanol, then with diethyl ether and dried to yield 155.4 g (85%) of the title compound.

III - 2-bromoacetamido-3-(2-chlorobenzoyl)-6-ethoxycarbonyl 4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene.



Into a five litre reactor fitted with appropriate means and with a separating funnel, were poured 2.5 litres of chloroform and 146 g (0.400 mol) of (II). 87.7 g (0.43 mol) of bromoacetylbromide contained in the separating funnel were added dropwise. The reaction mixture was stirred for one hour at room temperature and then washed with 300 ml of iced water. The organic phase was dried with anhydrous magnesium sulphate and filtered. The chloroform was evaporated off and the residue was treated with ethanol. The resulting precipitate was filtered off, washed with ethanol, then with diethyl ether, and dried to yield 184.6 g (95%) of the title compound.

IV - **2-aminoacetamido-3-(2-chlorobenzoyl)-6-ethoxy-carbonyl-4,5,6,7-tetrahydro-pyrido [3,4-b] thiophene.**

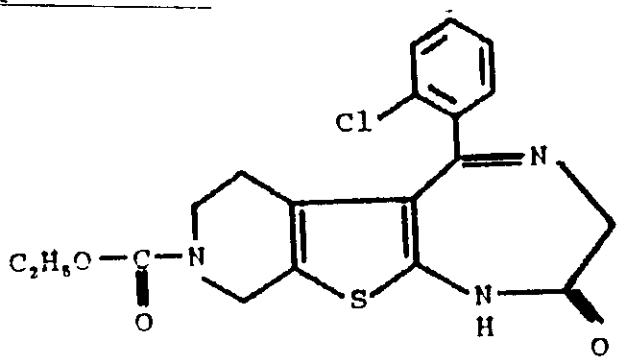


Into a five litre reactor fitted with a gas-injector were poured 174.8 g (0.36 mol) of (III) and 3 litres of THF. The suspension was cooled to 0°C and then gaseous ammonia previously dried over potassium hydroxide was added. The addition was conducted in 8 hours. (60 g of ammonia were absorbed). The mixture was stirred overnight at 0°C. 2 litres of THF were then evaporated off under reduced pressure, and 750 ml of ethyl acetate were added. After decantation, the organic phase was washed once with 300 ml of a 10% sodium chloride solution, three times with 300 ml of water, and dried

with anhydrous magnesium sulphate. After filtration, the solvent was partially evaporated off using a rotary evaporator. The precipitate was allowed to stand overnight in a refrigerator.

After filtration, the precipitate was washed with diethyl ether and dried to give 119 g of the title compound. The remaining organic phase was concentrated and treated with a mixture of 1.5 litres of diethyl ether:THF (3:1 by volume) to give 14.6 g of the title compound (overall yield 88%).

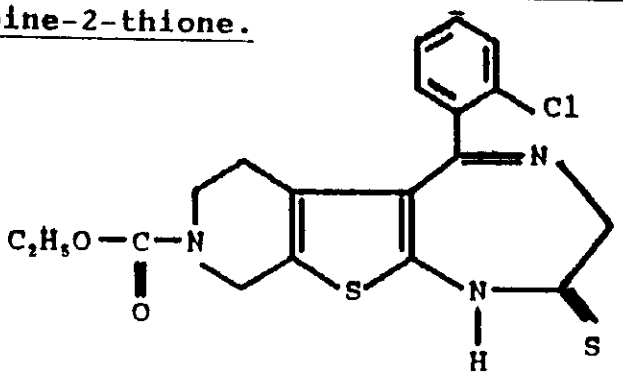
V - 5-(2-chlorophenyl)-8-ethoxycarbonyl-6,7,8,9-tetrahydro-3-H-pyrido [4',3' : 4,5] thieno [3,2-E] 1,4--diazepine-2-one.



126.6 g (0.3 mol) of (IV) and 800 ml of pyridine were poured into a two litre-reactor fitted with stirring, cooling and warming means and under nitrogen circulation. The reaction mixture was refluxed for 18 hours. After having checked that all the starting material had reacted, the pyridine was partially evaporated off using a rotary evaporator under reduced pressure.

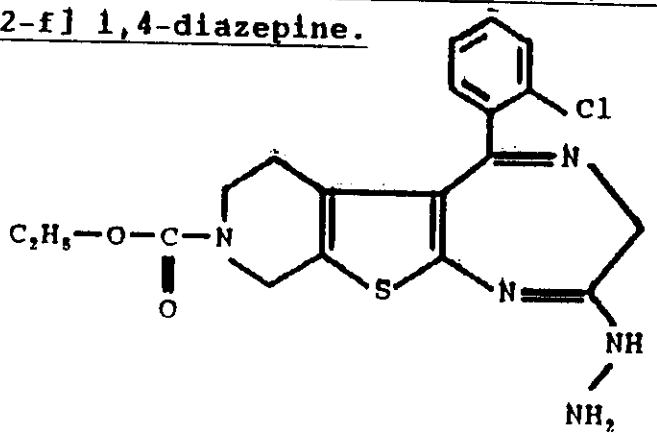
The dark brown oil obtained was dissolved in 1 litre of ethanol. After cooling in an ice-bath, there was obtained a precipitate which was filtered off, washed with ethanol and diisopropyloxide to yield 101.3 g (83.6%) of the title compound.

VI -5- (2-chlorophenyl)-8-ethoxycarbonyl-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4--diazepine-2-thione.



93 g (0.230 mol) of V and 1.75 litres of pyridine were poured into a three litre-reactor fitted with appropriate means. After solubilization, there were added 56.3 g (0.25 mol) of phosphorus pentasulphide, and the reaction mixture was then stirred for three hours at 80-85°C. Thereafter, the pyridine was evaporated off and the obtained residue treated with icy-water. The mixture was then extracted by methylene dichloride, dried with anhydrous magnesium sulphate, filtered, evaporated and treated with diethyl ether. The resulting product was filtered off, and treated with 700 ml of acetonitrile. The suspension was heated at 60°C for 30 minutes and then allowed to cool. After filtration, and washing with acetonitrile and then with diethyl ether, the residue was dried to yield 80.2 g (83%) of the title compound.

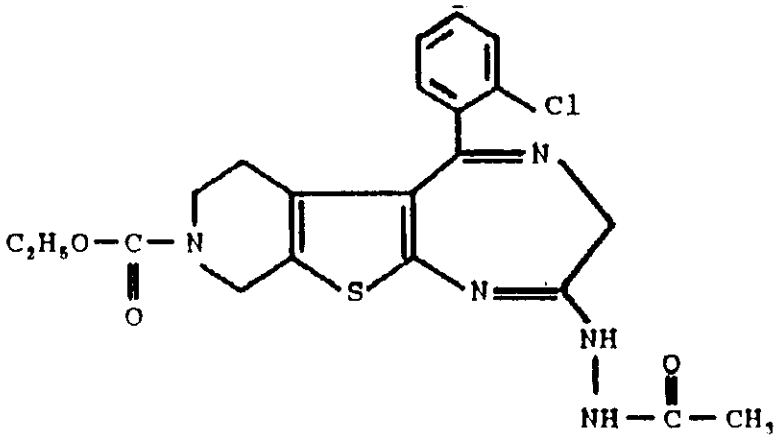
VII -5-(2-chlorophenyl)-8-ethoxycarbonyl-2-hydrazino--6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine.



73.5 g (0.175 mol) of VI and 1 litre of methanol were poured into a two litre reactor fitted with appropriate means and with a separating funnel. 26.4 ml (0.525 mol) of hydrazine hydrate contained in the separating funnel were then added at room temperature and the mixture was stirred for two hours at room temperature.

Thereafter 1/7 of the methanol were evaporated off at 30°C and the residue was allowed to crystallize overnight in a refrigerator. After filtration, washing with diethyl ether and drying, there was obtained 65.1 g of the title compound (yield 89%).

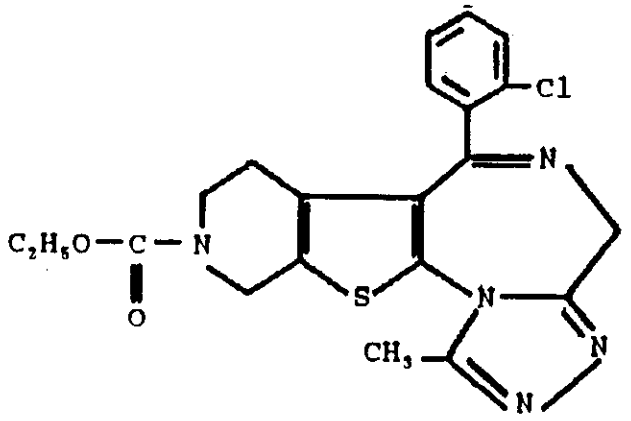
VIII - 5-(2-chlorophenyl)-8-ethoxycarbonyl-2-acetamido-amino-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine.



58.5 g (0.140 mol) of VII and 1 litre of THF were poured into a two litre reactor fitted with cooling means and under nitrogen circulation. 11 g (0.140 mol) of acetyl chloride and 150 ml of THF were then added. The addition was conducted in 30 minutes at 0°C. The solution became red after stirring for 45 minutes. The THF was then evaporated off and the resulting residue treated with iced water. Then 17.5 g of sodium bicarbonate were added and the mixture was extracted with 1 litre of methylene dichoride. The organic phase was washed once with water and dried with anhydrous magnesium sulphate.

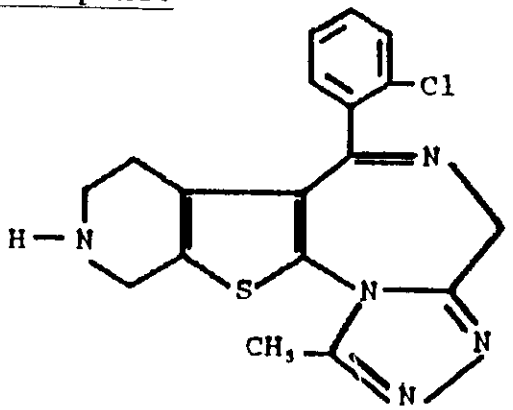
After filtration, the solvent was evaporated off and the resulting residue treated with diethyl ether, filtered and dried to yield 54.1 g (84%) of the title compound.

IX - 6-(2-chlorophenyl-9-(ethoxycarbonyl)-7,8,9,10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine.



46.9 g (0.102 mol) of VIII and 750 ml of acetic acid were poured into a two litre reactor fitted with appropriate means and under nitrogen circulation. The red solution was slowly warmed over one hour to reflux temperature and then refluxed for 15 minutes. The yellow solution was then concentrated on a rotary evaporator at a bath temperature not exceeding 35°C, and the acetic acid was extracted with 700 ml of toluene. The residue was then treated with diethyl ether, filtered, washed with diethyl ether, and dried to yield 42.8 g (95%) of the title compound.

X - 6-(2-chlorophenyl)-7,8,9,10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine.



500 ml of mixture of hydrobromic acid:acetic acid (30% hydrobromic acid by volume) were poured into a one litre-reactor fitted with appropriate means. Then 35.8 g (0.081 mol) of IX were added portionwise at 5°C and the mixture was stirred at room temperature for five days (CCM analysis showed traces of starting material). Thereafter, 250 ml of acetic acid were evaporated off and the compound precipitated. 250 ml of diethyl ether were added and the mixture was stirred for 30 minutes. The precipitate was filtered off, washed with diethyl ether and poured into a one litre flask in which 500 ml of iced water were added. The pH was adjusted to 9.5 with addition of a 40% aqueous sodium hydroxide solution. The reaction temperature was maintained below 20°C. After extraction with dichloromethane, the organic phase was dried with anhydrous magnesium sulphate, filtered and the dichloromethane was partially evaporated off. Then 120 ml of ethyl acetate were added with stirring. After precipitation, 160 ml of diethyl ether was added and the mixture was allowed to crystallize overnight in a refrigerator. After filtration and washing with diethyl ether, there were obtained 28.1 g of the title compound (yield 93.6%).

The following Examples illustrate the invention.

EXAMPLE 1 :

6 -(2-chlorophenyl)- 9-(isopropylthiomethylcarbonyl)-7,8,9,10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = isopropyl.

Into a one litre reactor fitted with stirring, cooling and warming means and placed under nitrogen circulation were poured 30 ml of dimethylformamide, 20.3 g (0.055 mol) of 6-(2-chlorophenyl)-7, 8, 9, 10 -tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine and 8.9 g (0.058 mol) of isopropyl-thio-acetic acid. After cooling the mixture to 0°C, there were slowly added, under stirring, 12.36 g (0.058 mol) of dicyclohexylcarbodiimide. Stirring was maintained for 4 hours at 0°C and then for one hour after the reaction mixture had reached room temperature. There were then added 2 g of dicyclohexylcarbodiimide and the mixture was stirred overnight.

The dimethylformamide was evacuated off by a mild warming (< 60°C) under reduced pressure. The residue was treated with 500 ml of dichloromethane, washed once with water, twice with a 10 % aqueous sodium bicarbonate solution, and twice with a 10 % aqueous solution of citric acid, dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was then dissolved in 200 ml of ethanol and crystallized. Yield 22.2 g (83 %).

EXAMPLE 2 :

6 -(2-chlorophenyl)- 9-(isopropylthiomethyl-thiocarbonyl)-7,8,9,10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S R = isopropyl.

Into the same reactor as in Example 1 were poured, under nitrogen circulation, 300 ml of toluene, 12.2 g (0.025 mol) of the product of Example 1 and 4.75 g (0.0117 mol) of Lawesson's reagent. The reaction mixture was slowly warmed over two hours to reflux temperature and reflux was maintained for two hours. After evaporation to dryness and treatment with dichloromethane, the solution was passed on a silica gel column, eluting with dichloromethane:methanol 95:5 by volume. After evaporation to dryness of the resulting solution, the residue was recrystallized from methanol. Yield 10.2 g (82 %).

The following compounds have been prepared as described in Examples 1 and 2, but starting with the appropriate $RSCH_2COOH$ derivative.

EXAMPLE 3 :

6-(2-chlorophenyl)-9-(t.butylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O R = t.butyl.

EXAMPLE 4 :

6-(2-chlorophenyl)-9-(t.butylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = t.butyl.

EXAMPLE 5 :

6-(2-chlorophenyl)-9-(hexadecylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = hexadecyl.

EXAMPLE 6 :

6 -(2-chlorophenyl)- 9-(hexadecylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = hexadecyl.

EXAMPLE 7 :

6-(2-chlorophenyl)- 9-(phenylthiomethyl-carbonyl)- 7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = phenyl.

EXAMPLE 8 :

6-(2-chorophenyl)-9- (phenylthiomethyl-thiocarbonyl) -7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = phenyl.

EXAMPLE 9 :

6-(2-chlorophenyl)- 9-(4-methoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 4-methoxyphenyl.

EXAMPLE 10 :

6-(2-chlorophenyl)-9-(4-methoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 4-methoxyphenyl.

EXAMPLE 11 :

6- (2-chlorophenyl)- 9-(3,4-dimethoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 3,4-dimethoxyphenyl.

EXAMPLE 12 :

6 -(2-chlorophenyl)- 9-(3,4-dimethoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 3,4-dimethoxyphenyl.

EXAMPLE 13 :

6-(2-chlorophenyl)- 9-(3, 4, 5-trimethoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 3,4,5-trimethoxyphenyl.

EXAMPLE 14 :

6-(2-chlorophenyl)-9-(3,4,5-trimethoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 3,4,5-trimethoxyphenyl.

EXAMPLE 15 :

6-(2-chlorophenyl)-9-(2,3,4-trimethoxyphenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 2,3,4-trimethoxyphenyl.

EXAMPLE 16 :

6 -(2-chlorophenyl)- 9-(2,3,4-trimethoxyphenylthiomethyl--thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 2,3,4-trimethoxyphenyl.

EXAMPLE 17 :

6-(2-chlorophenyl)- 9-(4-t.butylphenylthiomethyl-carbonyl)--7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 4-t.butylphenyl.

EXAMPLE 18 :

6 -(2-chlorophenyl)- 9-(4-t.butylphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 4-t.butylphenyl.

EXAMPLE 19 :

6 -(2-chlorophenyl)- 9-(2-trifluoromethylphenylthiomethyl--carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O, R = 2-trifluoromethylphenyl.

EXAMPLE 20 :

6 -(2-chlorophenyl)- 9-(2-trifluoromethylphenylthiomethyl--thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S, R = 2-trifluoromethylphenyl.

EXAMPLE 21 :

6 -(2-chlorophenyl)- 9-(3-trifluoromethylphenylthiomethyl--carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O, R = 3-trifluoromethylphenyl.

EXAMPLE 22 :

6 -(2-chlorophenyl)- 9-(3-trifluoromethylphenylthiomethyl--thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S, R = 3-trifluoromethylphenyl.

EXAMPLE 23 :

6 -(2-chlorophenyl)- 9-(4-trifluoromethylphenylthiomethyl--carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O, R = 4-trifluoromethylphenyl.

EXAMPLE 24 :

6 -(2-chlorophenyl)- 9-(4-trifluoromethylphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S, R = 4-trifluoromethylphenyl.

EXAMPLE 25 :

6 -(2-chlorophenyl)- 9-(4-fluorophenylthiomethyl-carbonyl)--7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O, R = 4-fluorophenyl.

EXAMPLE 26 :

6 -(2-chlorophenyl)- 9-(4-fluorophenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S, R = 4-fluorophenyl.

EXAMPLE 27 :

6 -(2-chlorophenyl)- 9-(2,3-dichlorophenylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = O, R = 2,3-dichlorophenyl.

EXAMPLE 28 :

6 -(2-chlorophenyl)- 9-(2,3-dichlorophenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine

Y = S, R = 2,3-dichlorophenyl.

EXAMPLE 29 :

6 -(2-chlorophenyl)- 9-(4-phenoxyphenylthiomethyl-carbonyl) -7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 4-phenoxyphenyl.

EXAMPLE 30 :

6 -(2-chlorophenyl)-9 -(4-phenoxyphenylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 4-phenoxyphenyl.

EXAMPLE 31 :

6 -(2-chlorophenyl)- 9-(2- furylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 2-furyl.

EXAMPLE 32 :

6 -(2-chlorophenyl)- 9-(2- furylthiomethyl-thiocarbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 2-furyl.

EXAMPLE 33 :

6 -(2-chlorophenyl)- 9-(2- thienylthiomethyl-carbonyl)-7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = O, R = 2-thienyl.

EXAMPLE 34 :

6 -(2-chlorophenyl)- 9-(2- thienylthiomethyl-thiocarbonyl)- - 7, 8, 9, 10-tetrahydro-1-methyl-4H-pyrido [4',3':4,5] thieno [3,2-f] 1,2,4-triazolo [4,3-a] 1,4-diazepine
Y = S, R = 2-thienyl.

TOXICITY

The compounds of the invention are not toxic on mice at the dose of 1 g /kg, by the IP or oral routes.

PHARMACOLOGY

Various pharmacological determinations have been made on these compounds ; they are summarized as follows :

1) Inhibition of platelet agregation induced by PAF

This experimentation was conducted according to the method of R. KINLOUGH. RATHBONE, J.P. CAZENAVE, M. PACKHAM and F. MUSTARD, Lab. Invest. 48, 98, 1980. In this test, New Zealand rabbits were used (male New Zealand rabbits of an average weight of 5 kg).

The determinations are made on a chrono-log Coultronics agregometer, at 57°C coupled with a graphic recorder ; the results of these determinations (in molecular concentration) are reported in Table I (central column).

2) Inhibition of the binding to benzodiazepine receptors

The interest of the previous experimentation depends on the results obtained in this experimentation : as a compound of the invention has a benzodiazepine like structure, it is important to check whether the specific benzodiazepine activity would not appear at the dose where platelet agregation was inhibited.

Therefore, this experimentation has been conducted according to the method of MOHLER H. and RICHARD J.G. Agonist and antagonist benzodiazepine receptor interaction in vitro, Nature, vol. 294, 763-765, 1981.

This experimentation was conducted on rat brains incubated 1 h 30 at 4°C using ^{3}H-RO-15-1788 and ^{3}H-RO-5-4864 (NEN) as tracers and RO-15-4788 and RO-5-4864 as reference antagonists.

The results in molecular concentration are reported in Table I (right hand column).

3) Global ischemia on gerbils

For this test, males gerbils were anaesthetized with brietal at the doses of 35 mg/kg IP ; thereafter, both carotides were clamped for 10 minutes, then the clamping was released. Treated animals received each 10 mg/kg of the compounds of one of the examples.

One week later, the animals were killed and both hippocampes were taken, weighed and frozen at -80°C.

After crushing with 1 ml of TRIS-HCl pH 7.4 for 30 seconds, aliquots of 50 µl each of this preparation were incubated in each 1 ml of TRIS-HCl buffer containing ^{3}H-PK 11195 at 2 nM (90 Ci/mmole, NENE, Germany) for 1 hour at 25°C.

For each preparation, 3 determinations were made. The density of omega 3 sites (marked by the specific ^{3}H-PK 11195 marker) are expressed in f-moles of PK 11195/mg of fresh tissues and converted in percentage of protection compared to control.

The results of this experimentation are reported in Table II.

PRESENTATION - POSOLOGY

In human therapy, the compounds of the invention are preferably administered by the oral route. Preferred forms of administration include tablets, gelatine capsules and the like. Usual posology is from 50 mg to 500 mg per diem according to the case. The preferred unit dose is 50 mg, associated with appropriate carriers and agents. They may also be administrated by injection route. Usual posology is from 5 mg to 100 mg per diem according to the case. Unit doses are from 1 to 20 mg.

TABLE I A

EXAMPLES	IC_{50}		BDZ receptors	
1	2.53	10^{-8}	6.7	10^{-6}
2	2.81	10^{-8}	4.82	10^{-5}
3	1.68	10^{-8}	2.3	10^{-6}
4	4.97	10^{-7}	1.55	10^{-6}
5	7.43	10^{-9}	1.21	10^{-7}
6	9.46	10^{-9}	9.1	10^{-7}
7	5.11	10^{-7}	2.1	10^{-6}
8	1.05	10^{-8}	7.33	10^{-6}
9	3.37	10^{-8}	2.7	10^{-6}
10	1.71	10^{-7}	6.6	10^{-5}
11	2.64	10^{-8}	1.4	10^{-6}
12	3.14	10^{-8}	8.7	10^{-7}

TABLE I B

EXAMPLES	IC_{50}	BDZ receptors
13	$1.85\ 10^{-8}$	$5.5\ 10^{-5}$
14	$9.22\ 10^{-9}$	$1.5\ 10^{-6}$
15	$1.2\ 10^{-7}$	$3.6\ 10^{-6}$
16	$5.35\ 10^{-8}$	$6.\ 10^{-7}$
17	$8.75\ 10^{-9}$	$4.7\ 10^{-6}$
18	$2.3\ 10^{-8}$	$4.41\ 10^{-5}$
19	$6.36\ 10^{-9}$	$2.7\ 10^{-7}$
20	$1.46\ 10^{-7}$	$1.6\ 10^{-6}$
21	$8.66\ 10^{-9}$	$8.1\ 10^{-7}$
22	$8.18\ 10^{-9}$	$6.1\ 10^{-7}$
23	$1.24\ 10^{-8}$	$1.2\ 10^{-6}$
24	$3.27\ 10^{-8}$	$3.3\ 10^{-6}$

TABLE I C

EXAMPLES	IC_{50}		BDZ receptors	
25	1.13	10^{-8}	6.3	10^{-7}
26	6.56	10^{-9}	6.1	10^{-7}
27	8.45	10^{-9}	4.8	10^{-5}
28	9.06	10^{-9}	4.3	10^{-6}
29	9.05	10^{-9}	1.23	10^{-6}
30	1.04	10^{-7}	3.6	10^{-7}
31	7.10	10^{-9}	2.3	10^{-7}
32	8.75	10^{-9}	1.3	10^{-6}
33	4.12	10^{-8}	5.7	10^{-6}
34	1.28	10^{-7}	7.2	10^{-7}

TABLE II A

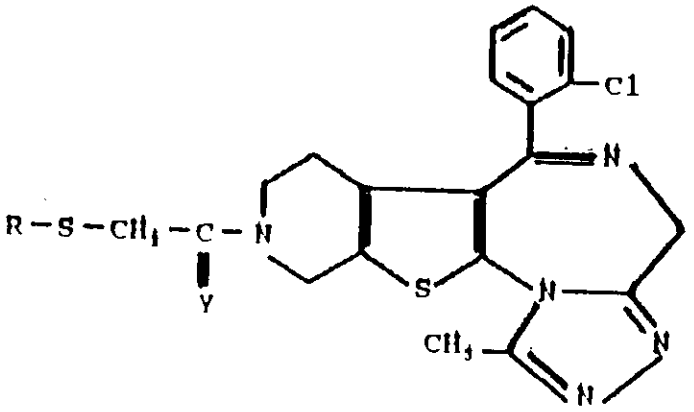
EXAMPLES	Global protection in %
1	54.2 ***
2	36.3 **
3	34.3 **
4	38.1 **
5	29.4 **
6	27.8 **
7	14.8 NS
8	26.2 *
9	31.2 **
10	10.3 NS
11	46.5 ***
12	34.1 **
13	32.1 **
14	19.7 NS
15	35.8 **
16	29.3 **
17	11.1 NS
18	12.6 NS
19	45.6 ***
20	32.7 **

TABLE II B

EXAMPLES	Global protection in %
21	34.1 **
22	48.1 ***
23	37.5 **
24	38.7 **
25	14.7 NS
26	26.5 *
27	33.3 **
28	35.3 **
29	51.6 ***
30	16.1 NS
31	36.2 **
32	30.3 **
33	24.8 *
34	34.7 **

CLAIMS:

1. A thieno-triazol -diazepine derivative of the general formula I



I

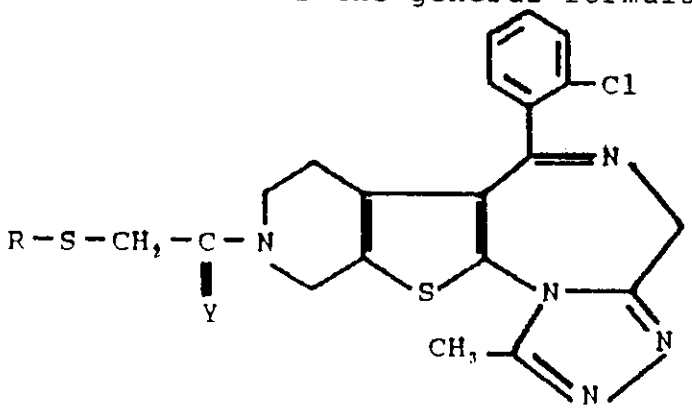
wherein Y represents an oxygen or sulphur atom and R represents a straight chain or branched chain alkyl group having from 1 to 20 carbon atoms; a phenyl group; a phenyl group substituted by one or more of a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms, an alkoxy group having from 1 to 5 carbon atoms, a halogen atom, a trifluoromethyl group or an optionally substituted phenoxy group; or a furyl or thienyl group;
or a therapeutically acceptable salt of such a derivative.

2. A thieno-triazolo-diazepine derivative according to claim 1 in which Y represents an oxygen atom and R represents an isopropyl, t-butyl, hexadecyl, phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxy--phenyl, 2,3,4-trimethoxyphenyl, 4-t.butylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylkphenyl, 4-fluorophenyl, 2,3-dichloro--phenyl, 4-phenoxyphenyl, 2-furyl or 2-thienyl group.

3. A thieno-triazolo-diazepine derivative according to claim 1 in which Y represents a sulphur atom and R represents an isopropyl, t-butyl, hexadecyl, phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4,5-trimethoxy--phenyl, 2,3,4-trimethoxyphenyl, 4-t.butylphenyl,

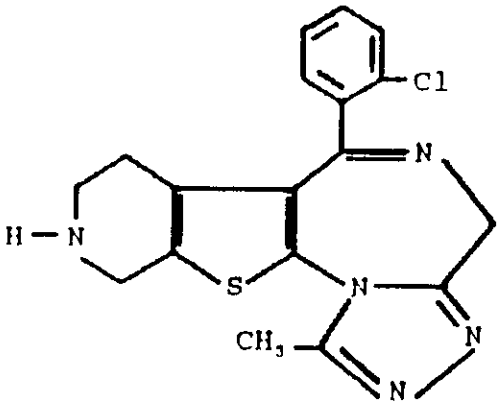
2-trifluoromethyl, 3-trifluoromethylphenyl 4-trifluoromethylkphenyl, 4-fluorophenyl, 2,3-dichloro--phenyl, 4-phenoxyphenyl, 2-furyl or 2-thienyl group.

4. A process for the preparation of a thieno-triazolo--diazepine derivative of the general formula I



I

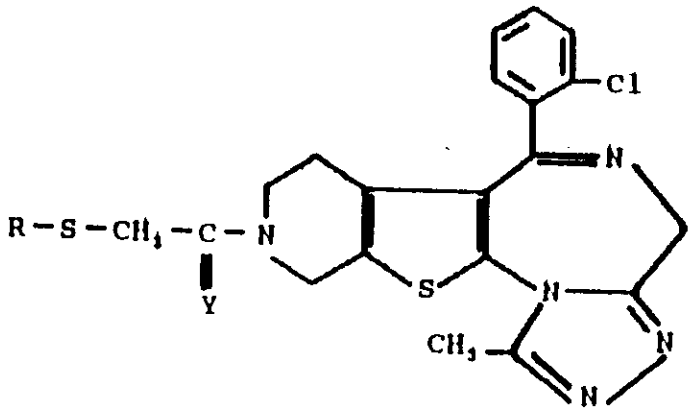
wherein Y represents an oxygen atom and R is as defined in claim 1, the process comprising treating the thieno--triazolo-diazepine compound of the formula II



II

with a compound of the general formula $RSCH_2COOH$ wherein R is as defined in claim 1, under nitrogen circulation, in the presence of a slight stoichiometric excess of hydroxy-benzotriazole or dicyclohexylcarbodiimide, at about 0°C.

5. A process for the preparation of a thieno-triazolo--diazepine derivative of the general formula I



I

wherein Y represents a sulphur atom and R is as defined in claim 1, the process comprising treating the corresponding thieno-triazolo-diazepine derivative of the general formula I wherein Y represents an oxygen atom with Lawesson's reagent or with phosphorus pentasulphide in an aprotic solvent at a temperature of from room temperature to the reflux temperature of the reaction mixture.

6. A therapeutic composition comprising a thieno--triazolo-diazepine derivative according to any of claims 1 to 3, or a therapeutically acceptable salt of such a derivative, in admixture with a therapeutically acceptable diluent or carrier.

7. A therapeutic composition according to claim 6, for oral administration in a single dose, containing from 10 to 100 mg of active ingredient.

8. A therapeutic composition according to claim 6, for parenteral administration in a single dose, containing from 1 to 20 mg of active ingredient.

REGISTER ENTRY FOR GB2231330

Form 1 Application No GB9010403.5 filing date 09.05.1990

Priority claimed:
13.05.1989 in United Kingdom - doc: 8911030

Title THIENO-TRIAZOLO-DIAZEPINE DERIVATIVES

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Classified to
C2C
C07D A61K

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Publication No GB2231330 dated 14.11.1990

Examination requested 28.08.1990

Patent Granted with effect from 29.04.1992 (Section 25(1)) with title
THIENO-TRIAZOLO-DIAZEPINE DERIVATIVES

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER	GB2231330

PROPRIETOR(S)

Societe de Conseils de Recherches et d'Applications Scientifiques (S C R A S), Incorporated in France, 51/53 rue du Docteur Blanche, 75016 Paris, France

DATE FILED	09.05.1990
DATE GRANTED	29.04.1992
DATE NEXT RENEWAL DUE	09.05.1994
DATE NOT IN FORCE	
DATE OF LAST RENEWAL	
YEAR OF LAST RENEWAL	00
STATUS	PATENT IN FORCE