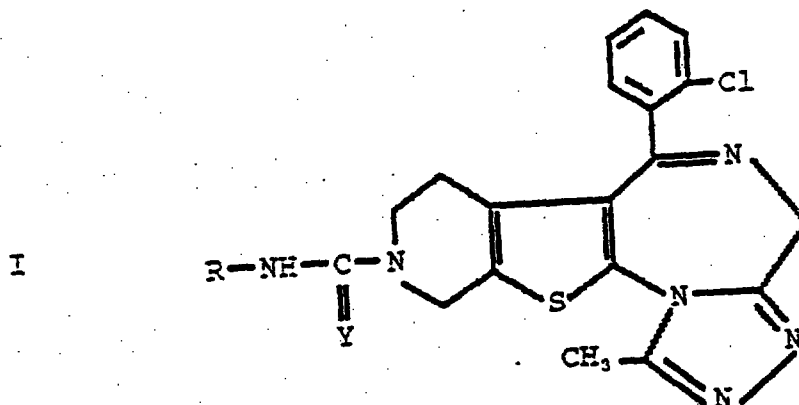


TITLE:Thieno-triazolo-diazepine DerivativesDESCRIPTION:

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-asthmatic and anti-allergic agents and gastro-intestinal protectors.

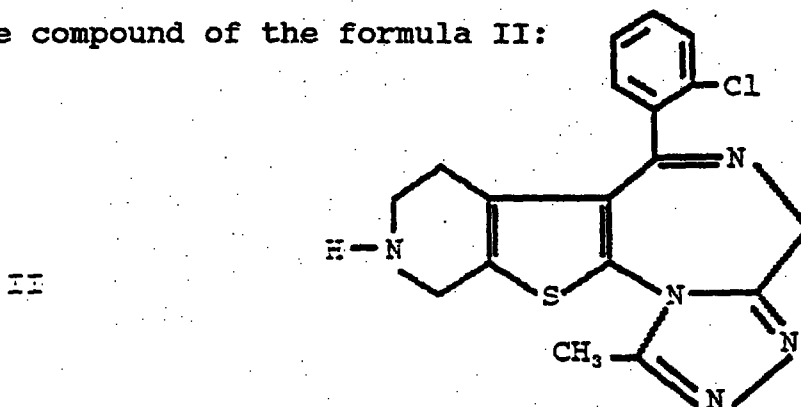
The invention provides thieno-triazolo-diazepine derivatives of the general formula I:



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 cycloalkyl group having from 3 to 6 carbon atoms, a straight chain alkenyl group having from 2 to 5 carbon atoms, a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms and being substituted by an aryl or heteroaryl group, a phenyl group substituted by one or more of an alkyl group, a lower alkoxy group having from 1 to 5 carbon atoms, a phenoxy group, an alkylsulphonyl group having from 1 to 5 carbon atoms, a fluorine atom, a chlorine atom or a trifluoromethyl group,

a heterobicyclic group, or
a sulphonyl group substituted by a phenyl group, a heteroaryl group, a morpholino group, or a bicyclic group;
with the proviso that if Y represents an oxygen atom then R does not represent a cycloalkyl, pyridylalkyl or pyranylalkyl group;
and further provides therapeutically acceptable salts of such a derivative.

The invention also provides a process for the preparation of the said compounds, the process comprising reacting under nitrogen circulation a molar excess of the thieno-triazolo-diazepine compound of the formula II:



with a compound of the general formula $R-N=C=Y$ wherein R and Y are as above defined, in an aprotic solvent. Generally the reaction is started at room temperature but 1/2 to 3 hours at 60-70°C may be necessary to complete the reaction.

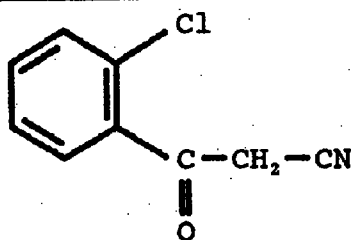
The invention further provides a therapeutic composition comprising a thieno-triazolo-diazepine derivative of the general formula I or a therapeutically acceptable salt thereof in admixture with a therapeutically acceptable diluent or carrier.

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.

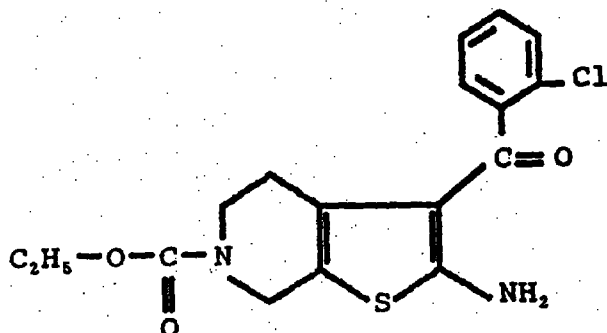


7 litres of anhydrous tetrahydrofuran (THF) and 115.9 g (1.36 mol) of previously dried cyanoacetic acid were poured into an appropriate reactor under nitrogen circulation at -70°C . 1715 ml (2.74 mol) of a 1.6 M solution of butyllithium in hexane was added dropwise, while allowing the temperature to 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

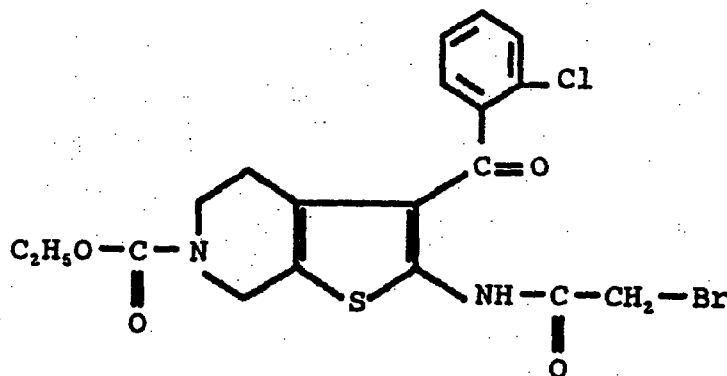
filtered off, and washed with hexane to give 97.2 g of the title compound (yield 79%).

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



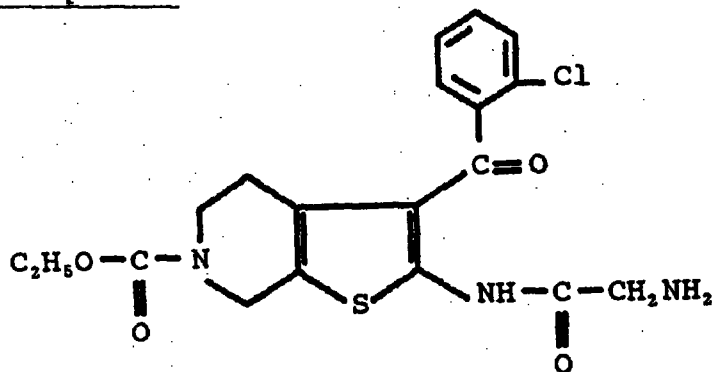
Into a two litre erlen flask fitted with a cooler, were poured 85.5 g (0.501 mol) of N-carbethoxy-4-piperidone, 90 g (0.501 mol) of (I), 19.3 g (0.600 mol) of flowers of sulphur and 44.4 g (0.501 mol) of morpholine, in 550 ml of methanol. The mixture was refluxed for one hour. After evaporation of 250 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-bromo-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 bromoacetyl bromide 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.

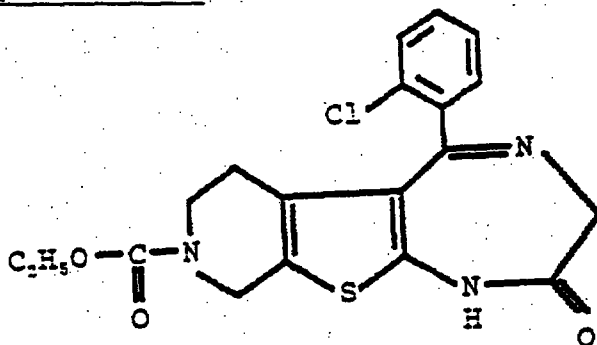


Into a five litre reactor fitted with a gas-injector were poured 174.8 g (0.36 mol) of (III) and 3 litres of THF. The suspension was cooled to 0°C and then gaseous ammonia previously dried over potassium hydroxide was added. The addition was conducted in 8 hours. (60 g of ammonia were absorbed). The 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%).

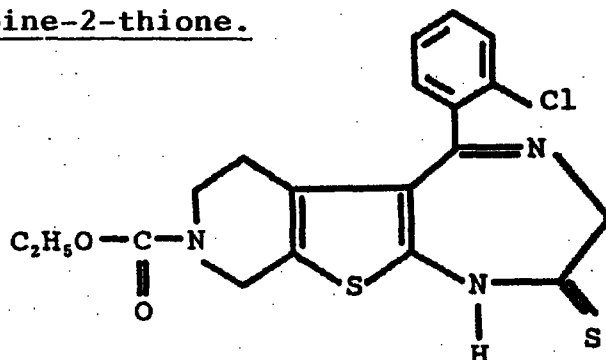
V - 5-(2-chlorophenyl)-8-ethoxycarbonyl-6,7,8,9-tetrahydro-3-H-pyrido [4',3' : 4,5] thieno [3,2-f] 1,4-diazepine-2-one.



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.

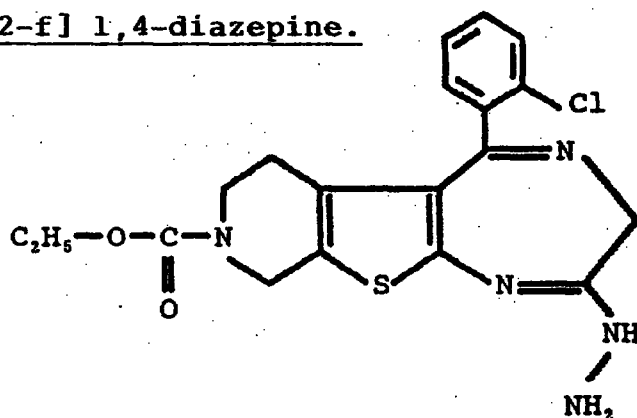
The dark brown oil obtained was dissolved in 1 litre of ethanol. After cooling in an ice-bath, there was obtained a precipitate which was filtered off, washed with ethanol and diisopropyl ether to yield 101.3 g (83.6%) of the title compound.

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.

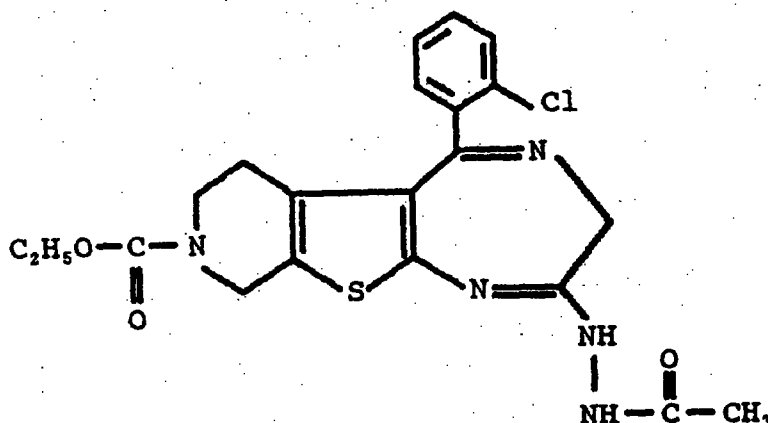
VII -5-(2-chlorophenyl)-8-ethoxycarbonyl-2-hydrazino-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5] thieno [3,2-f] 1,4-diazepine.



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%).

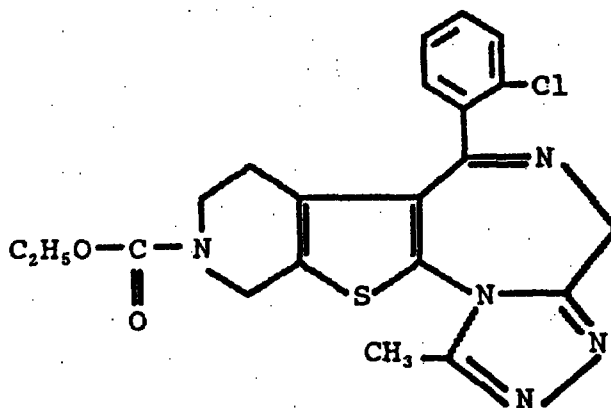
VIII - 5-(2-chlorophenyl)-8-ethoxycarbonyl-2-acetamido-
amino-6,7,8,9-tetrahydro-3H-pyrido [4',3':4,5]
thieno [3,2-f] 1,4-diazepine.



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 dichloride. The organic phase was washed once with water and dried with anhydrous magnesium sulphate.

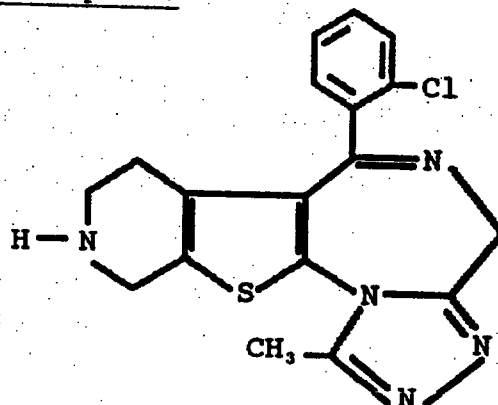
After filtration, the solvent was evaporated off and the resulting residue treated with diethyl ether, filtered and dried to yield 54.1 g (84%) of the title compound.

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-isopropylthiocarbamoyl-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 a 1 litre reactor, under nitrogen circulation, were poured 650 ml of pure benzene, 26.85 g (172 mmoles) 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, then dropwise a solution of 7.6 g (75 mm) of isopropylisothiocyanate, dissolved in 25 ml of pure benzene. The addition was conducted in about 15 minutes and the temperature rose from 15° to 25°C. After stirring the reacting mixture for 3 hours at room temperature, it was heated to 60-70°C, and then refluxed for 15 minutes. After cooling, filtration, washing with benzene, and washing twice with diethyl ether, the compound was dried. It was then dissolved in 250 ml of acetone and refluxed for about 15 minutes. After cooling, filtration, washing twice with acetone and twice with diethyl ether, the compound was separated and dried overnight at 60°C under reduced pressure. There were obtained 34 g of the title compound (Yield 91%). Melting point 205-206°C (Tottoli); white powder.

The following compounds have been prepared as described in Example 1, but starting with the appropriate isocyanate or isothiocyanate derivative.

EXAMPLE 2 :

6-(2-chlorophenyl) - 9-isopropylcarbamoyl - 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

EXAMPLE 3 :

6-(2-chlorophenyl) - 9-t.butylcarbamoyl - 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.butylthiocarbamoyl - 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-hexadecylthiocarbamoyl - 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 6 :

6-(2-chlorophenyl) - 9-(4-methoxyphenylcarbamoyl) - 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 7 :

6-(2-chlorophenyl) - 9-(4-methoxyphenylthiocarbamoyl) - 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 8 :

6-(2-chlorophenyl) - 9-(3,4,5-trimethoxyphenylcarbamoyl) -
-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 9 :

6-(2-chlorophenyl) - 9-(3,4,5-trimethoxyphenylthiocarbamoyl)-
- 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 10 :

6-(2-chlorophenyl) - 9-(4-t.butylphenylcarbamoyl) - 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 11:

6-(2-chlorophenyl) - 9-(4-t.butylphenylthiocarbamoyl)-
-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 12 :

6-(2-chlorophenyl) - 9-(2-trifluoromethylphenylthiocarbamoyl)-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 13 :

6-(2-chlorophenyl) - 9-(3-trifluoromethylphenylthiocarbamoyl)-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 14 :

6-(2-chlorophenyl) - 9-(4-trifluoromethylphenylcarbonyl)-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 15 :

6-(2-chlorophenyl) - 9-(4-trifluoromethylphenylthiocarbamoyl)-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 16 :

6-(2-chlorophenyl) - 9-(4-fluorophenylthiocarbamoyl)-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 17 :

6-(2-chlorophenyl) - 9-(2,3-dichlorophenylcarbamoyl) - 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 18 :

6-(2-chlorophenyl) - 9-(4-phenoxyphenylcarbamoyl) - 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 19 :

6-(2-chlorophenyl) - 9-(α -methylphenethylthiocarbamoyl) -
-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 = α -methylphenethyl

EXAMPLE 20 :

6-(2-chlorophenyl) - 9-(β -methylphenethylthiocarbamoyl) -
-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 = β -methylphenethyl

EXAMPLE 21 :

6-(2-chlorophenyl) - 9-(4-methylsulphonyl phenylthiocarbamoyl) -
- 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-methylsulphonylphenyl

EXAMPLE 22 :

6-(2-chlorophenyl) - 9-(2,4-di-t.butylphenylthiocarbamoyl)-
- 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 = 2,4-di-t.butylphenyl

EXAMPLE 23 :

6-(2-chlorophenyl) - 9-benzylcarbamoyl - 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 = benzyl

EXAMPLE 24 :

6-(2-chlorophenyl) - 9-(2-furfurylthiocarbamoyl) - 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-furfuryl

EXAMPLE 25 :

6-(2-chlorophenyl) - 9-(3-quinolylthiocarbamoyl) - 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-quinolyl

EXAMPLE 26 :

6-(2-chlorophenyl) - 9-cyclohexylthiocarbamoyl - 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 = cyclohexyl

EXAMPLE 27 :

6-(2-chlorophenyl) - 9-allylthiocarbamoyl - 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 = allyl

EXAMPLE 28 :

6-(2-chlorophenyl) - 9-(2,4-difluorophenylcarbamoyl) - 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 = 2,4-difluorophenyl

EXAMPLE 29 :

6-(2-chlorophenyl) - 9-(phenylsulphonylthiocarbamoyl) - 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 = phenylsulphonyl

EXAMPLE 30 :

6-(2-chlorophenyl) - 9-(2-furylsulphonylthiocarbamoyl) - 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-furylsulphonyl

EXAMPLE 31 :

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

EXAMPLE 32 :

6-(2-chlorophenyl) - 9-(2-pyrrolylsulphonylthiocarbamoyl)-
-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-pyrrolylsulphonyl

EXAMPLE 33 :

6-(2-chlorophenyl) - 9-(3-pyridylsulphonylcarbamoyl) - 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- pyridyl sulphonyl

EXAMPLE 34 :

6-(2-chlorophenyl) - 9-(4-quinolylsulphonylthiocarbamoyl) -
-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- quinolylsulphonyl

EXAMPLE 35 :

6-(2-chlorophenyl) - 9-(4-morpholinylsulphonylcarbamoyl) -
-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- morpholinylsulphonyl

TOXICITY

The compounds of the invention are not toxic on mice per os at the dose of 1 g/kg. By the IP route on the mice, only the compounds of Examples 10, 17, 18 and 32 showed a LD₅₀ between 0.4 and 1 g/kg and all the others were not toxic at 1 g/kg.

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 ³H-RO-15-1788 and ³H-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) Action on the bronchospasm induced by the PAF

The PAF intravenous injection in anaesthetized guinea-pigs induces a bronchoconstriction with a leucopeny and a thrombocytopeny, according to the method described in S. DESQUAND, C. TOUVAY, J. RANDON, V. LAGENTE, B. VILAIN, I. MARIDONNEAU-PARINI, A. ETIENNE, J. LEFORT, P. BRAQUET and B. VARGAFTIG. Interference of BN 52021 (Ginkgolide B) with the bronchopulmonary effects of PAF-acether in the guinea-pig. Eur. J. Pharmacol. 127 : 83-95, 1986.

Male Hartley guinea-pigs (400-450 g) (Charles River) anaesthetized with urethane (2 g/kg IP), then are thracheotomized and submitted to a forced respiration with a breathing pump : 70-80 strokes/mn, 1 ml of air/100 g per stroke. A catheter is introduced in the jugular vein for the injections, an other is introduced in the carotic artery for blood takings. The initial resistance is kept constant under the pressure of 10 cm of water in accordance with the Konzett and Rössler method and the air in excess is measured with a transducor for bronchospasm UGO BASILE together with an enregistror GEMINI. The guinea-pigs had received an IV injection of pancuronium (Pavulon) to inhibit their spontaneous respiration.

The compound according to the invention and the reference compound Apafant have been prepared as suspension in gummy water and administered orally 1 hour before the stimulation by the PAF.

The bronchoconstriction is determined by the calculation of the percentage of bronchoconstriction $\frac{A}{B} \times 100$ wherein A

stands for induced bronchoconstriction in mm and B stands for maximum bronchoconstriction in mm.

The results are reported in table II.

PRESENTATION - POSOLOGY

In human therapy, the compounds of the invention are preferably administered by 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.

In a form suitable for oral administration in a single dose, the therapeutic composition of the invention may contain from 10 to 100 mg of active ingredient.

Preferred unit dose is 50 mg, associated with appropriate carriers and agents.

TABLE I-A

EXAMPLES	IC ₅₀	Benzodiazepine Receptors
1	3.28×10^{-8}	7×10^{-6}
2	2.35×10^{-8}	6.6×10^{-5}
3	1.71×10^{-8}	4.3×10^{-7}
4	8.82×10^{-9}	1.35×10^{-7}
5	2.97×10^{-7}	6.3×10^{-5}
6	1.27×10^{-7}	7.7×10^{-5}
7	3.01×10^{-7}	2×10^{-6}
8	1.15×10^{-8}	1.5×10^{-6}
9	3.87×10^{-8}	4.5×10^{-6}
10	8.8×10^{-9}	5.25×10^{-6}
11	9.44×10^{-9}	1.2×10^{-6}
12	1.71×10^{-7}	3.5×10^{-6}

TABLE I-B

EXAMPLES	IC ₅₀	Benzodiazepine Receptors
13	1.71×10^{-7}	6.25×10^{-6}
14	1.5×10^{-7}	7.05×10^{-5}
15	2.2×10^{-7}	1.25×10^{-6}
16	6.4×10^{-8}	7×10^{-7}
17	5.5×10^{-8}	9.2×10^{-7}
18	3.3×10^{-8}	8.6×10^{-7}
19	4.25×10^{-8}	3.6×10^{-7}
20	6.17×10^{-9}	7.2×10^{-7}
21	2.4×10^{-8}	1.1×10^{-6}
22	3.66×10^{-7}	6.3×10^{-7}
23	6.68×10^{-8}	1.6×10^{-6}
24	4.8×10^{-8}	6.5×10^{-7}

TABLE I-C

EXAMPLES	IC ₅₀	Benzodiazepine Receptors
25	1.82×10^{-7}	3.5×10^{-7}
26	5.33×10^{-8}	4.1×10^{-6}
27	9.05×10^{-9}	1.4×10^{-7}
28	5.86×10^{-8}	2.2×10^{-7}
29	1.1×10^{-8}	6.3×10^{-7}
30	8.15×10^{-9}	6.15×10^{-7}
31	6.66×10^{-8}	4.33×10^{-6}
32	2.05×10^{-7}	9.1×10^{-6}
33	1.0×10^{-7}	4×10^{-5}
34	3.4×10^{-8}	2.2×10^{-6}
35	6.10×10^{-9}	7.25×10^{-6}

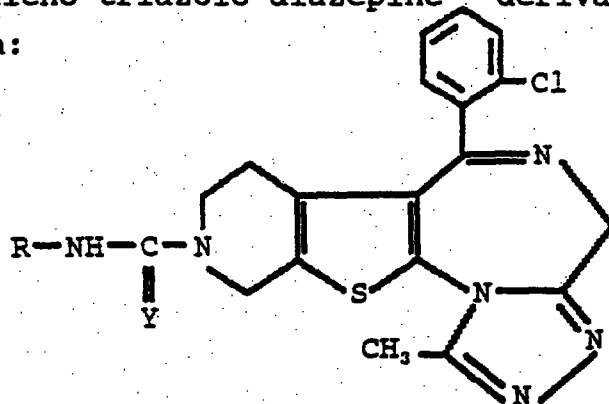
TABLE II

Examples	Percentage of bronchoconstriction	Percentage of action
Controls	79. $\pm$ 5.55	-
Apafant	25.3 $\pm$ 11.56	- 68.0
1	23.4 $\pm$ 10.50	- 70.4
3	28.7 $\pm$ 9.30	- 63.7
5	30.3 $\pm$ 8.80	- 61.6
7	13 $\pm$ 4.39	- 83.5
8	16.2 $\pm$ 8.38	- 79.5
10	26.7 $\pm$ 11.0	- 66.2
14	48.6 $\pm$ 14.32	- 38.5
18	14.1 $\pm$ 11.25	- 81.8
22	25.5 $\pm$ 13.2	- 67.7
24	33.3 $\pm$ 12.8	- 57.9
29	37.2 $\pm$ 14.95	- 52.9
32	22.4 $\pm$ 9.8	- 71.7



CLAIMS

1. A thieno-triazolo-diazepine derivative of the general formula:



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 cycloalkyl group having from 3 to 6 carbon atoms,
a straight chain alkenyl group having from 2 to 5 carbon atoms,
a straight chain or branched chain alkyl group having from 1 to 5 carbon atoms and being substituted by an aryl or heteroaryl group,
a phenyl group substituted by one or more of an alkyl group,
a lower alkoxy group having from 1 to 5 carbon atoms, a phenoxy group, an alkylsulphonyl group having from 1 to 5 carbon atoms, a fluorine atom, a chlorine atom or a trifluoromethyl group,
a heterobicyclic group, or
a sulphonyl group substituted by a phenyl group, a heteroaryl group, a morpholino group, or a bicyclic group;
with the proviso that if Y represents an oxygen atom then R does not represent a cycloalkyl, pyridylalkyl or pyranalkyl group;
or a therapeutically acceptable salt of such a derivative.

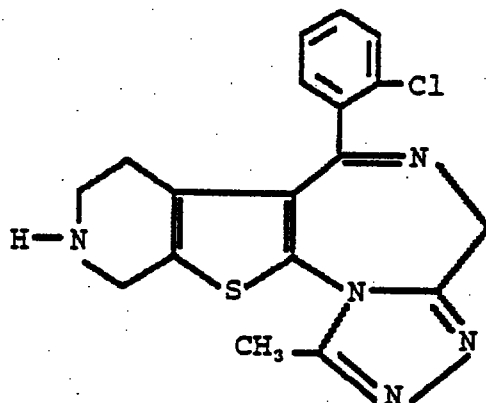
2. A thieno-triazolo-diazepine derivative according to claim 1 in which Y represents an oxygen atom and R represents an isopropyl, t.butyl, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl, 4-t.butylphenyl,



4-trifluoromethylphenyl, 2,3-dichlorophenyl,
4-phenoxyphenyl, benzyl, 2,4-difluorophenyl,
2-thienylsulphonyl, 3-pyridylsulphonyl or
4-morpholinylsulphonyl 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, 4-methoxyphenyl, 3,4,5-trimethoxyphenyl, 4-t.butylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-fluorophenyl, α -methylphenethyl, β -methylphenethyl, 4-methylsulphonylphenyl, 2,4-di-t.butylphenyl, 2-furfuryl, 3-quinolyl, cyclohexyl, allyl, phenylsulphonyl, 2-furylsulphonyl, 2-pyrrolylsulphonyl or 4-quinolylsulphonyl group.

4. A process for the preparation of a compound according to claim 1, the process comprising reacting under nitrogen circulation a molar excess of the thieno-triazolo-diazepine compound of the formula:



with a compound of the general formula $R-N=C=Y$ wherein R and Y are as defined in claim 1, in an aprotic solvent and at a temperature comprised between room temperature and 70°C.



5. A process according to claim 4 in which the reaction is started at room temperature and completed by $\frac{1}{2}$ to 3 hours at from 60 to 70°C.

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.
