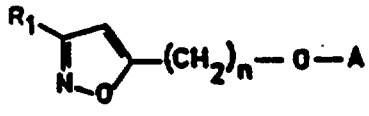
The invention relates to novel antivirally active substituted isoxazole derivatives, a process for their preparation, pharmaceutical products containing these compounds and their use.

Phenyl-aliphatic isoxazole derivatives are described in European Specifications EP-A 0,111,345 and EP-A 0,137,242 which are antivirally active.

Thieno-aliphatic isoxazole derivatives have now been found which likewise have antiviral activity.

The invention therefore relates to novel substituted isoxazole derivatives of the general formula (I)



I

in which

R_1 denotes (C_1-C_4)-alkyl,

n denotes an integer 6, 7 or 8

A denotes a group of the general formulae (II) or (III)



II or III

and

R_2 denotes hydrogen or methyl,

a process for their preparation, pharmaceutical products containing these compounds and their use.

The expression "(C_1-C_4)-alkyl" used in this description means straight-chain or branched hydrocarbon groups with 1 to 4 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, butyl or tert.-butyl.

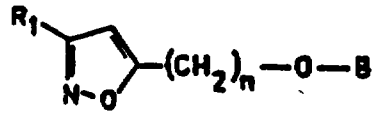
In a preferred group of compounds of the formula (I), R_1 denotes methyl or ethyl, methyl being particularly preferred. R_2 is preferably hydrogen and n preferably represents the number 7.

A particularly preferred group within the compounds of the general formula (I) is that in which A denotes a 5-(4,5-dihydro-2-oxazolyl)-thienyl group of the

formula (II) bonded to the isoxazolyl-alkoxy radical in the alpha-position to the sulphur atom.

Particularly preferred individual compounds are 5-(7-(5-(4,5-dihydro-2-oxazolyl)-2-thienyl)oxyheptyl)-3-methyl-isoxazole and 5-(7-(2-(4,5-dihydro-2-oxazolyl)-4-thienyl)oxyheptyl)-3-methyl-isoxazole.

The isoxazole derivatives of the general formula I can be prepared according to the invention by cyclizing a compound of the general formula (IV)

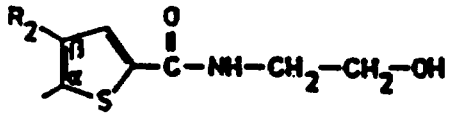


IV

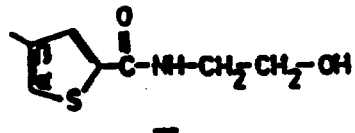
in which

R_1 and n are as defined above,

B denotes a group of the general formulae (V) or (VI)



V



VI

and

R_2 is as defined above, by treatment with a dehydrating reagent, to form the oxazole ring.

The reaction according to the invention can be carried out in the presence or absence of an inert organic solvent.

If the reaction is carried out in the presence of a solvent, examples of suitable solvents are hydrocarbons, such as benzene, toluene or xylene, halogenated hydrocarbons, such as chloroform, chlorobenzene, methylene chloride or carbon tetrachloride, ethers, such as dioxane, tetrahydrofuran, dimethylformamide, or mixtures of such solvents. Possible dehydrating agents here are the reagents usually employed for such cyclization reactions, for example phosphorus oxychloride, phosphorus pentachloride or thionyl

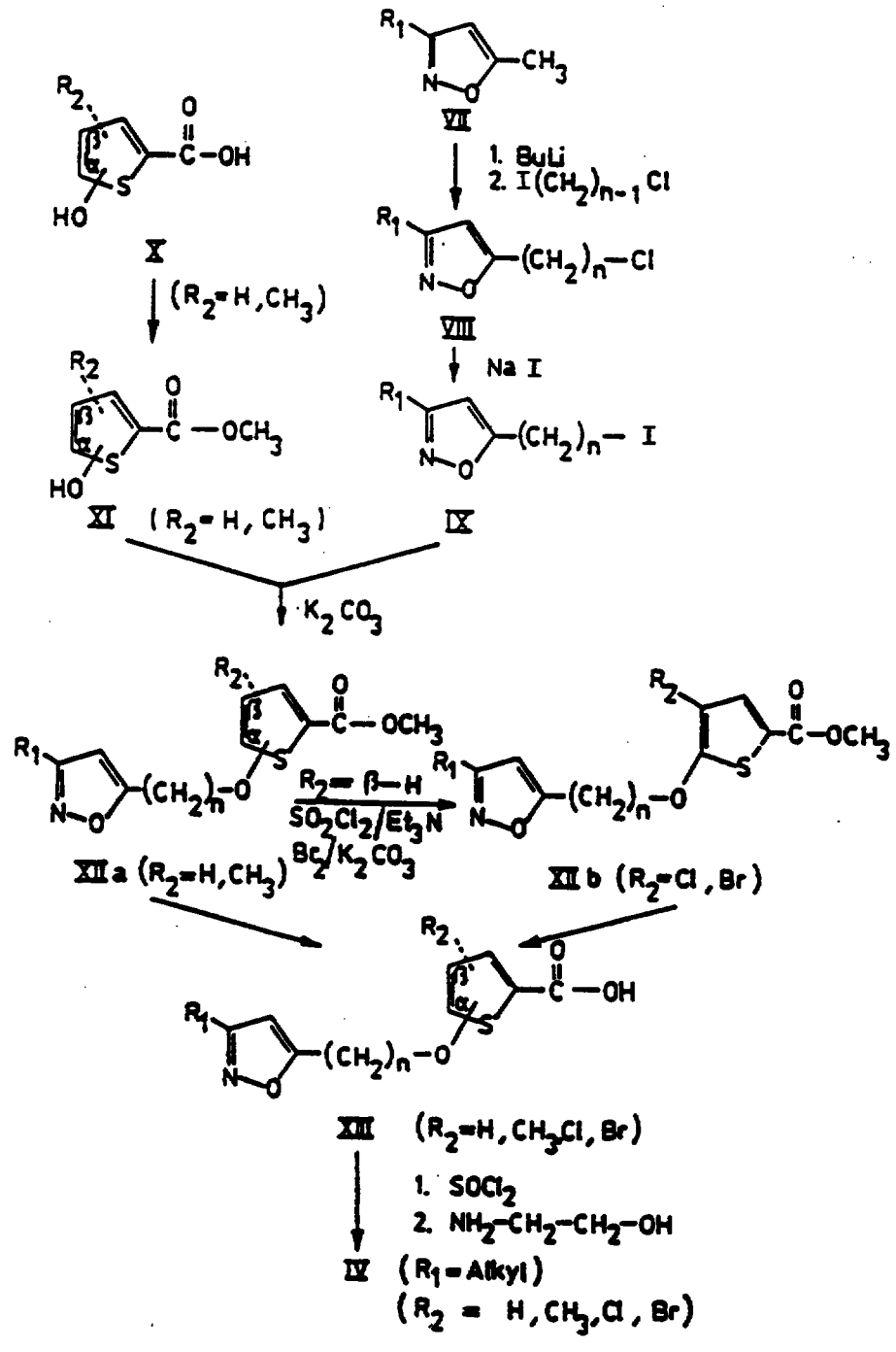
chloride. The dehydrating reagent can be employed for this in equivalent amounts or in a slight excess, for example in amounts of 1.1 to 3 mol per mol of the compound of the formula (IV). The reaction is carried out at -20°C to +10°C, preferably at -5°C to +5°C.

In a particularly preferred embodiment of the process according to the invention, the compounds of the general formula (IV) are in general cyclized in the absence of a separate solvent by treatment with an excess of a liquid, dehydrating reagent, which simultaneously serves as the solvent, at -30°C to +10°C, preferably -5°C to +5°C and especially preferably in an icebath at about 0°C. Suitable reagents for this purpose are again phosphorus oxychloride or thionyl chloride, the use of thienyl chloride having proved to be especially advantageous.

The starting compounds of the general formula (IV) used for the process according to the invention can be prepared in a manner which is known per se, starting from known products. In particular, the starting compounds can be synthesized in accordance with the following equation and the specific statements in the examples.

In the following equation, R_1 and n have the same meaning as defined above. According to the reaction sequence shown in the equation, both compounds of the general formula (IV) in which B denotes a group of the formula (V) and compounds of the general formula (IV) in which B denotes a group of the formula (VI) can be synthesized. The hydroxy- or isoxazolyl-alkoxy radical is accordingly either in the alpha- or beta-position in the formulae (X), (XI), (XIIa) and (XIII) of the equation, and if this occupies the alpha-position, any radical R_2 present is bonded to the thienyl group in the beta-position.

Equation


1. BuLi
2. I(CH2)n-1Cl
Na I
(R2=H,CH3)
K2CO3
R2=β-H
SO2Cl2/Et3N
Br2/K2CO3
XIIa (R2=H,CH3)
XIIb (R2=Cl,Br)
XIII (R2=H,CH3,Cl,Br)
1. SOCl2
2. NH2-CH2-CH2-OH
IV (R1=Alkyl)
(R2 = H,CH3,Cl,Br)

The compounds of the general formula (I) have an anti-infective action, and in particular a pronounced antiviral action. These useful pharmacological properties can be determined in vitro and in vivo using standard methods. The compounds of the general formula (I) thereby exhibit an outstanding action in particular against various types of enteroviruses, picornaviruses and rhinoviruses, and can therefore be employed in human medicine for the treatment and prophylaxis of virus diseases.

The following test methods were used to investigate the antiviral properties:

Serial three-fold dilutions of solutions of the substances under investigation in MEM (minimum essential medium) were prepared in microtiter plates with a flat bottom. The same volumes of the particular virus dilutions in MEM and cell suspension in MEM with 15% FCS (fetal calf blood serum) were added. The cell concentration here was chosen such that a confluent cell lawn was formed after 1 - 2 days. The virus dilutions were adjusted so that a complete cytopathic effect occurred after 3 - 4 days, without the addition of an inhibiting substance.

As controls, cells (cell control), cells with virus (virus control) and cells with the test substances in various concentration (toxicity control) were also run. The substance concentration at which a cell density which was still lower than in the cell control was observed was determined as the minimum toxic concentration (MTC).

The test substances were dissolved in dimethylsulphoxide and the solutions were diluted in MEM and suspended thoroughly by means of ultrasound.

The compounds according to the invention were investigated for their antiviral action in a representative cross-section of rhinoviruses of the type B1-55, echoviruses type B-9 and polioviruses type 2 and the minimum inhibitory concentration (MIC in ug/ml) was thereby determined.

In this virus inhibition test, known as a standard method, the MIC values shown in Table 1 were determined for compounds of the general formula (I), such as, for example, 5-(7-(5-(4,5-dihydro-2-oxazolyl)-2-thienyl)-oxyheptyl)-3-methyl-isoxazole (compound A) or 5-(7-(2-(4,5-dihydro-2-oxazolyl)-4-thienyl)oxyheptyl)-3-methyl-isoxazole (compound B).

Table 1

Antiviral action in vitro of compounds of the general formula (I).

Organism Serotype		Minimum inhibitory concentration (MIC, µg/ml)	
		Compound A	Compound B
Rhinotype	3	0.03	0.1
	16	0.3	1.0
	26	0.3	1.0
	32	1.0	3.0
	37	0.03	0.03
	48	0.1	1.0
	55	0.3	0.3
Echotype	B-9	0.03	1.0
Poliotype	2	0.1	1.0
MTC[1]		10	10

[1] Minimum toxic concentration

Compared with conventional compounds with antiviral properties, the compounds according to the invention have the advantage of improved lipophilic properties, which allow the blood-brain barrier to be overcome.

The compounds of the general formula (I) can be used as medicines, for example in the form of pharmaceutical products which contain them as a mixture with a pharmaceutical, organic or inorganic inert auxiliary and/or excipient material suitable for enteral or parenteral administration, such as, for example, pharmaceutically acceptable solvents, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols or vaseline.

The pharmaceutical products can be in solid form, for example as tablets, coated tablets, suppositories or

capsules, in semi-solid form, for example as ointments, or in liquid form, for example as solutions, suspensions or emulsions. If appropriate, they are sterilized and contain auxiliaries, such as preservatives, stabilizers or emulsifiers, salts for modifying the osmotic pressure and the like.

In particular, pharmaceutical products can contain the compounds according to the invention in combination with other therapeutically useful substances, for example with other anti-infective or antiviral active compounds. The compounds according to the invention can be formulated with these, together with the abovementioned auxiliaries and/or excipients, to give combination products.

The following examples illustrate the invention in more detail:

Example 1:

5-(7-(5-(4,5-Dihydro-2-oxazolyl)-2-thienyl)oxyheptyl)-3-methyl-isoxazole

0.60 g (1.64 mmol) of N-(2-hydroxyethyl)-5-(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylic acid amide (IV) is introduced into 2.5 ml of thionyl chloride at 0°C, the mixture is stirred at 0°C for 15 minutes and the excess thionyl chloride is then removed in vacuo. The residue is partitioned between saturated sodium bicarbonate solution and ethyl acetate. The mixture is extracted twice more with ethyl acetate and the combined organic phases are dried over sodium sulphate/active charcoal and evaporated.

The crude product (0.52 g of yellowish crystals) is purified by column chromatography (1:35, silica gel 60, particle size 0.040-0.063; eluting agent: ethyl acetate: petroleum ether = 3:1).

Yield: 0.29 g of colourless crystals (50.7% of theory)

Melting point = 69 - 70°C (diisopropyl ether)

The starting material can be prepared as follows:

5-(7-Chloroheptyl)-3-methyl-isoxazole (VIII)

21.0 g (0.216 mol) of 3,5-dimethylisoxazole (VII, prepared in accordance with the method of C. Kashima et

al., Bull.Chem.Soc.Jap.46, 310, 1973) are dissolved in 200 ml of absolute tetrahydrofuran, the solution is cooled to -80°C and 160 ml of n-butyllithium (1.35 M solution in n-hexane, 0.216 mol) are added dropwise at this temperature in the course of 40 minutes. The mixture is stirred at a temperature below -75°C for a further 15 minutes.

The reaction mixture is then added dropwise to a solution of 53.5 g (0.217 mol) of 1-iodo-6-chlorohexane (prepared in accordance with the method of W.F. Huber, J.Am.Chem.Soc. 73, 2730, 1951) in 150 ml of absolute tetrahydrofuran so that the temperature does not rise above -60°C. When the addition has ended, the mixture is stirred at -60°C for a further 15 minutes and allowed to warm to room temperature.

The reaction mixture is partitioned between methylene chloride and 0.2 N HCl, the aqueous phase is extracted three more times with methylene chloride and the combined organic phases are dried over sodium sulphate and evaporated.

The crude product (about 45 g) is distilled in portions in a bulb tube (air bath temperature 80°C/0.2 mbar).

Yield: 26.9 g of a yellowish oil

Methyl 5-(7-(3-methyl-5-isoxazolyl)heptyloxy)-2-thiophenecarboxylate (XIIa)

9.3 g (43.1 mmol) of 5-(7-chloroheptyl)-3-methylisoxazole and 7.12 g (47.4 mmol) of sodium iodide are heated under reflux in 60 ml of absolute acetone for 24 hours. The mixture is then cooled, the NaCl which has precipitated out is filtered off with suction and washed with a little acetone, and 7.16 g (45.3 mmol) of methyl 5-hydroxy-2-thiophenecarboxylate (XI) and 13.1 g (94.8 mmol) of potassium carbonate are added to the filtrate. The mixture is heated under reflux for 2 hours, cooled and largely evaporated. The residue is partitioned between water and ether and the aqueous phase is extracted twice with ether. The combined organic phases are washed with a little saturated sodium bisulphite

solution, dried over sodium sulphate/active charcoal and evaporated.

The crude product (11.9 g; 82% of theory) is recrystallized from diisopropyl ether.

Yield: 5.2 g of pale pink crystals (35.5% of theory)
Melting point 55-56°C (diisopropyl ether)

5-(7-(3-Methyl-5-isoxazolyl)heptyloxy)-2-thiophenecarboxylic acid (XIII)

0.98 g (2.90 mmol) of methyl 5-(7-(3-methyl-5-isoxazolyl)heptyloxy)-2-thiophenecarboxylate is heated under reflux in 8 ml of ethanol and 4 ml of water, and 0.18 g (3.19 mmol) of KOH, dissolved in 6 ml of water and 4 ml of ethanol, is added dropwise to this solution in the course of 10 minutes. The mixture is then heated under reflux for a further 2.5 hours.

After cooling, the mixture is largely evaporated, the residue is partitioned between water and ether and the aqueous phase is acidified to pH 1.5 with 2N HCl. The mixture is extracted three times with a total of 80 ml of ether and the combined organic phases are dried over sodium sulphate/active charcoal and evaporated.

Yield: 0.90 g of colourless crystals (95.8% of theory)
Melting point 96-7°C (diisopropyl ether)

N-(2-Hydroxyethyl)-5(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylic acid amide (IV)

2 ml of thionyl chloride are slowly added dropwise to 0.81 g (2.51 mmol) of 5-(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiopenecarboxylic acid, while cooling and stirring, a clear solution being formed. The solution is stirred at room temperature for a further 30 minutes and excess thionyl chloride is then removed in vacuo. The residue is dissolved in 6 ml of absolute methylene chloride, and a solution of 0.34 g (5.51 mmol) of ethanolamine in 5 ml of absolute methylene chloride is added dropwise at a temperature of 15°C. The mixture is stirred at room temperature for a further hour and concentrated somewhat and the concentrate is partitioned between water and ethyl acetate. The aqueous phase is extracted once more with a little ethyl acetate and the

combined organic phases are washed with water, dried over sodium sulphate/active charcoal and evaporated.
Yield: 0.81 g of yellowish crystals (88.2% of theory)
Melting point 107-110°C (acetonitrile)

Example 2:

5-(7-(2-(4,5-Dihydro-2-oxazolyl)-4-thienyl)oxyheptyl)-3-methyl-isoxazole

5 ml of thionyl chloride are introduced into 2.06 g (5.62 mmol) of N-(2-hydroxyethyl)-4-(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylic acid amide (IV) at 0°C, the mixture is stirred at 0°C for 10 minutes and the excess thionyl chloride is then removed in vacuo, without warming. The residue is partitioned between saturated sodium bicarbonate solution and ethyl acetate. Extraction is carried out twice more with ethyl acetate and the combined organic phases are dried over sodium sulphate/active charcoal and evaporated. The crude oil is purified by column chromatography (1 : 40, silica gel 60, particle size 0.040 to 0.063; eluting agent: ethyl acetate:petroleum ether = 3:1).
Yield: 0.52 g of yellowish crystals (26.5 of theory)
Melting point: 67 - 68°C (diisopropyl ether)

The starting material can be prepared as follows:

Methyl 4-hydroxy-2-thiophenecarboxylate (XI)

50.0 g (0.347 mol) of 4-hydroxy-2-thiophenecarboxylic acid and 58.3 g (0.694 mol) of sodium carbonate are heated to the boiling point in 990 ml of absolute 2-butanone under nitrogen, and 43.7 g (0.347 mol) of dimethyl sulphate are added dropwise in the course of 20 minutes. The mixture is heated under reflux for a further 2.5 hours. It is then evaporated in vacuo and the residue is partitioned between saturated sodium carbonate solution and ether. The aqueous phase is extracted five more times with 80 ml of ether each time. The combined organic phases are dried over sodium sulphate/active charcoal, filtered and evaporated.
Yield: 49.6 g of yellowish crystals (90%)
Melting point: 84 - 85°C (diisopropyl ether/petroleum ether)

5-(7-Iodoheptyl)-3-methyl-isoxazole (IX)

16.66 g (77.23 mmol) of 5-(7-chloroheptyl)-3-methyl-isoxazole (VIII) and 12.75 g (85.06 mmol) of sodium iodide NaI are heated under reflux in 110 ml of anhydrous acetone. A ^{1}H-NMR shows a conversion of about 85% after 7 hours and about 89% after 22 hours. After 27 hours, the mixture is concentrated and the residue is partitioned between methylene chloride and water (with the addition of a few ml of 2N hydrochloric acid). The aqueous phase is extracted by shaking several times with a total of 250 ml of methylene chloride and the organic phase is dried over sodium sulphate and evaporated.

Yield: 22.95 g of a brown liquid (96.7% of theory)

Methyl 4-(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylate (XIIa)

6.42 g (40.60 mmol) of methyl 4-hydroxy-2-thiophenecarboxylate (XI) and 11.88 g (38.67 mmol) of 5-(7-iodoheptyl)-3-methyl-isoxazole (IX) are heated under reflux with 5.34 g (40.60 mmol) of potassium carbonate (K_2CO_3) in 130 ml of anhydrous acetone for 8 hours. After the mixture has been left to stand overnight, it is concentrated, the residue is partitioned between 2N NaOH and ether and the aqueous phase is extracted several times with a total of 150 ml of ether. The organic phase is dried over sodium sulphate/active charcoal and evaporated.

Yield: 12.56 g of yellow crystals (96.3% of theory)

Melting point = 58-60C°C

4-(7-(3-Methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylic acid (XIII)

11.34 g (33.61 mmol) of methyl 4-(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylate are heated under reflux in 95 ml of ethanol and 45 ml of water, and 2.18 g (38.9 mmol) of KOH, dissolved in 70 ml of water and 46 ml of ethanol, are added dropwise to this solution. After the mixture has been heated under reflux for 3 hours, it is cooled and concentrated, the residue is partitioned between water and ether and the aqueous phase, after acidification to pH 1 with 2N HCl, is

extracted several times with ether. The combined organic phases are dried over sodium sulphate/active charcoal and evaporated.

Yield: 9.28 g of yellow crystals (85.6% of theory)

The crude product can be used directly in the next stage or can be recrystallized from diisopropyl ether, colourless crystals being obtained.

Melting point = 110-113°C

N-(2-Hydroxyethyl)-4-(7-(3-methyl-5-isoxazolyl)-heptyl-oxy)-2-thiophenecarboxylic acid amide (IV)

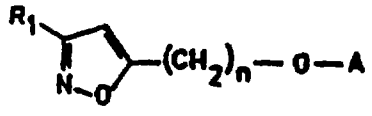
About 15 ml of thionyl chloride are added to 5.3 g (16.44 mmol) of 4-(7-(3-methyl-5-isoxazolyl)-heptyloxy)-2-thiophenecarboxylic acid at 0°C and the mixture is stirred at room temperature for 20 minutes. After filtration with suction under a waterpump vacuum, the residue is taken up in 40 ml of anhydrous methylene chloride and a solution of 2.2 g (36.09 mmol) of ethanolamine in 40 ml of anhydrous methylene chloride is added dropwise, with cooling. After the mixture has been stirred at room temperature for 2 hours, it is cooled and partitioned between water and methylene chloride, about 2N HCl being added for better separation of the phases. After shaking back the two phases, the organic phase is dried over sodium sulphate/active charcoal and evaporated.

Yield: 5.74 g of brown crystals (95.6% of theory)

Melting point: 56 - 57°C (crude product, can be used directly, without losses in yield, for the preparation of the compound of the formula I).

Patent Claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Substituted isoxazole derivatives of the formula (I)



I

in which
R_1 denotes (C_1-C_4)-alkyl,
n denotes an integer 6, 7 or 8,
A denotes a group of the formulae (II) and (III)



II or III

and
R_2 denotes hydrogen or methyl.

2. Compounds of the formula (I) according to Claim 1, in which A denotes a group of the formula (II).

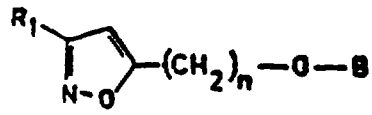
3. Compounds of the formula (I) according to either of Claims 1 and 2, in which R_1 denotes methyl and R_2 denotes hydrogen.

4. The compound 5-(7-(5-(4,5-dihydro-2-oxazolyl)-2-thienyl)oxyheptyl)-3-methyl-isoxazole according to Claim 1.

5. The compound 5-(7-(2-(4,5-dihydro-2-oxazolyl)-4-thienyl)oxyheptyl)-3-methyl-isoxazole according to Claim 1.

6. Process for the preparation of compounds according to Claim 1, characterized in that a compound of the formula (IV)

* C L M S *

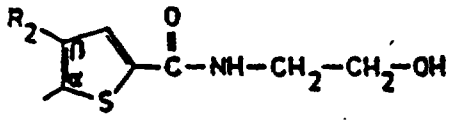


IV

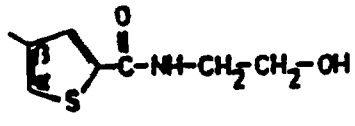
in which

R_1 and n are as defined above,

B denotes a group of the formulae (V) or (VI)



V



VI

and

R_2 is as defined above, is cyclized by treatment with a dehydrating reagent, to form the oxazole ring.

7. Pharmaceutical products containing compounds according to Claim 1 in combination with customary pharmaceutical auxiliaries and/or excipients.

8. Pharmaceutical products containing compounds according to Claim 1 in combination with other anti-infective or antiviral active compounds and customary pharmaceutical auxiliaries and/or excipients.

9. Use of the compounds according to Claim 1 for the preparation of medicaments for the treatment and prophylaxis of virus diseases.

* C L M S *