SPECIFICATION

Osmotic Device With Dual Thermodynamic Activity

This invention pertains to both a novel and unique delivery system. More particularly, the invention relates to an osmotic device comprising a wall formed in at least a part of a semi-permeable material that surrounds a compartment comprising: (1) a first osmotic composition comprising a beneficial agent, and preferably an osmagent and/or an osmopolyer, said composition in contacting arrangement with (2) a second osmotic composition comprising an osmagent and an osmopolymer. A passageway through the wall connects the exterior of the osmotic device with the first osmotic composition containing the beneficial agent for delivering the first composition from the osmotic device. The osmotic device is useful for delivering beneficial agents that because of their solubilities are difficult to deliver in a known amount at a controlled rate from an osmotic dispensing system.

Background of the Invention

Since the beginning of antiquity, both pharmacy and medicine have sought a delivery system for administering a beneficial drug. The first written reference to a dosage form is in the Eber Papyrus, written about 1552 B.C. The Eber Papyrus mentions dosage forms such as anal suppositories, vaginal pessaries, ointments, oral pill formulations, and other dosage preparations. About 2500 years passed without any advance in dosage form development, when the Arab physician Rhazes, 865—925 A.D., invented the coated pill. About a century later the Persian Avicenna, 980—1037 A.D., coated pills with gold or silver for increasing patient acceptability and for enhancing the effectiveness of the drug. Also around this time, the first tablet was described in Arabian manuscrips written by al-Zahrawi, 936—1009 A.D. The manuscrips described a tablet formed from the hollow impressions in two facing tablet molds. Pharmacy and medicine waited about 800 years for the next innovation in dosage forms, when in 1883 Mothes invented the capsule for administering drug. The next quantum leap in dosage forms came in 1972 with the invention of the osmotic delivery device by inventors Theeuwes and Higuchi as disclosed in United States Pat. Nos. 3,845,770 and 3,916,899. The osmotic devices disclosed in those patents comprise a semi-permeable wall that surrounds a compartment containing a useful agent. The wall is permeable to the passage of an external fluid, and it is substantially impermeable to the passage of useful agent. There is a passageway through the wall for delivering the useful agent from the osmotic device. These devices release useful agent by fluid being imbibed through the semi-permeable wall into the compartment at a rate determined by the permeability of the semi-permeable wall and the osmotic pressure gradient across the semi-permeable wall to produce an aqueous solution containing useful agent that is dispensed through the passageway from the device. These devices are extraordinarily effective for delivering a useful agent that is soluble in the fluid and exhibits an osmotic pressure gradient across the semi-permeable wall against the external fluid.

A pioneer advancement in osmotic delivery devices was presented to the dispensing arts by inventor Felix Theeuwes In United States Patent No. 4,111,202. In this patent, the delivery kinetics of the osmotic device is enhanced for delivering useful agents that are insoluble to very soluble in the fluid, by manufacturing the osmotic device with a useful agent compartment and an osmagent compartment separated by a film. The film is movable from a rested to an expanded state. The osmotic device delivers agent by fluid being imbibed through the semi-permeable wall into the osmagent compartment producing a solution that causes the compartment to increase in volume and act as a driving force that is applied against the film. This force urges the film to expand against the useful agent compartment and correspondingly diminish the volume of the useful agent compartment, whereby useful agent is dispensed through the passageway from the osmotic device. While this device operates successfully for its intended use, and while it can deliver numerous useful agents of varying solubilities, its use can be limited because of the manufacturing steps and costs needed for fabricating and placing the movable film in the compartment of the osmotic device.

In United States Patent No. 4,327,725 patentees Richard Cortese and Felix Theeuwes provided an osmotic dispensing device for delivering beneficial agents, that because of their solubilities in aqueous and biological fluids, are difficult to deliver in meaningful amounts at controlled rates over time. The osmotic devices of this patent comprise a semi-permeable wall surrounding a compartment containing a beneficial agent that is insoluble to very soluble in aqueous and biological fluids, and an expandable hydrogel. In operation the hydrogel expands in the presence of external fluid that enters the device thereby causing the beneficial agent to be dispensed through the passageway from the device. This device operates successfully for its intended use, and it delivers many difficult to deliver beneficial agents for their intended purpose. Now it has been observed, its use can be limited because the hydrogel lacks a present ability to imbibe sufficient fluid for the maximum self-expansion needed for urging the beneficial agent from the device.

It will be appreciated by those versed in the dispensing art, that if an osmotic device can be provided that exhibits a high level of osmotic activity for delivering a beneficial agent by generating in situ an expanding force sufficient for delivering the maximum amount of agent at a controlled rate from an osmotic device, such an osmotic device would have a positive value and represent an advancement in the dispensing art. Likewise, it will be immediately appreciated by those versed in the dispensing art

that if an osmotic device is made available possessing dual thermodynamic osmotic activity for delivering increased amounts of a beneficial agent, said osmotic device would find practical application in the fields of pharmacy and medicine.

Object of the Invention

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide an osmotic system that represents a further improvement and advancement in the dispensing art.

Another object of the invention is to provide an osmotic system manufactured in the form of an osmotic device for delivering in vivo a beneficial drug that is difficult to deliver and now can be delivered by the osmotic device provided by this invention in therapeutically effective amounts over time.

Another object of the invention is to provide an osmotic system possessing dual osmotic activity, which system comprises a compartment containing a first osmotic composition comprising a drug, and preferably an osmagent and/or an osmopolymer, and a second osmotic composition comprising an osmagent and an osmopolymer, with the compositions acting in concert for delivering the drug from the osmotic device.

Yet another object of the invention is to provide an osmotic device having means for high loading of a water-insoluble or a slightly water-soluble drug and means for delivering the drug in either instance at a controlled rate and continuously over time.

Yet another object of the invention is to provide an osmotic device that can deliver a pH dependent beneficial agent by providing a neutral medium for delivering the beneficial agent in a finely dispersed form for increasing its surface area and for maximizing the dissolution rate of the beneficial agent.

Still yet another object of the invention is to provide an osmotic system for delivering a drug having a very low dissolution rate that is the rate-limiting step for delivering the drug from the system, but now can be delivered by using an osmotic composition that functions in situ as a wetting agent and a solubilizing agent for increasing the dissolution rate and the solubility of the drug, thereby enhancing its delivery from the osmotic system.

Still yet another object of the invention is to provide an osmotic system comprising means for maintaining a high level of osmotic activity of a polymer used for delivering a beneficial agent from the osmotic system.

Still a further object of the invention is to provide an osmotic, therapeutic device that can administer a complete pharmaceutical dosage regimen comprising poorly soluble to very soluble agents, at a controlled rate and continuously, for a particular time period, the use of which requires intervention only for the initiation and possible termination of the regimen.

Other objects, features, aspects and advantages of the invention will be more apparent to those versed in the dispensing art from the following detailed specification taken in conjunction with the figures and the accompanying claims.

Brief Description of the Drawings

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Figure 1 is an isometric view of an osmotic device designed for orally administering a beneficial agent to the gastrointestinal tract;

Figure 2 is an opened view of the osmotic device of Figure 1 illustrating the structure of the osmotic device of Figure 1;

Figure 3 is an opened view of the osmotic device of Figure 1 illustrating the osmotic device in operation and delivering a beneficial agent from the osmotic device;

Figure 4 is an opened view of the osmotic device of Figure 1 considered with Figure 3 illustrating the osmotic device in operation and delivering a major amount of a beneficial agent from the osmotic device;

Figure 5 shows an osmotic therapeutic device with its wall partially broken away, designed for delivering a beneficial agent into a body passageway, such as the ano-rectal and vaginal passageways;

Figure 6 shows the osmotic device of Figure 5 with a different wall structure;

Figure 7 shows the osmotic device of Figure 5 depicting a different wall structure than the wall structure depicted in Figure 6.

Figure 8 represents the weight gain as a function of time for a polymer encapsulated in a semi-permeable membrane when the encapsulated polymer is placed in water;

Figure 9 depicts the cumulative amount of drug released from a device comprising an osmopolymer having two different molecular weights;

Figure 10 depicts the cumulative amount of drug released from a device using a different set of osmopolymers;

Figure 11 depicts the osmotic pressure curves for a number of osmagent and a number of osmopolymer/osmagent compositions;

Figure 12 depicts the cumulative release profile for an osmotic system using two different osmopolymers;

Figure 13 depicts the release rate per hour for an osmotic system different from Figure 9 containing an osmopolymer having two different molecular weights;

Figure 14 depicts the cumulative amount released from a single composition device comprising only one layer;

Figure 15 illustrates the in vivo and in vitro cumulative release for one drug delivered by the osmotic device;

Figure 16 illustrates the in vivo and in vitro cumulative release for a different drug delivered by an osmotic device.

In the drawings and the specification, like parts in related figures are identified by like parts. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further detailed elsewhere in the disclosure.

Detailed Description of the Drawings

Turning now to the drawings in detail, which are examples of various osmotic devices provided by the invention, and which examples are not to be construed as limiting, one example of an osmotic device is seen in Figure 1. In Figure 1, osmotic device 10 is seen comprising a body member 11 having a wall 12 and a passageway 13 for releasing a beneficial agent from osmotic device 10.

In Figure 2, osmotic device 10 of Figure 1 is seen in opened section. In Figure 2, osmotic device 10 comprises a body 11, a semipermeable wall 12 that surrounds and forms internal compartment 14, that communicates through a passageway 13 with the exterior of osmotic device 10. Compartment 14 contains a first osmotic composition comprising a beneficial agent 15, represented by dots, and it can be from insoluble to very soluble in fluid imbibed into compartment 14, an osmagent 16, represented by wavy lines, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across semi-permeable wall 12 against an external fluid, and, an osmopolymer 17, represented by horizontal dashes, that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across semi-permeable wall 12 against an exterior fluid present in the environment of use. Wall 12 is formed of a semi-permeable composition that is substantially permeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of agent 15, osmagent 16 and osmopolymer 17. Semi-permeable wall 12 is non-toxic and it maintains its physical and chemical integrity during the delivery life of device 10.

Compartment 14 also houses a second osmotic composition that is distant from passageway 13 and in contacting relation with the first composition. The second composition is an expandable driving force that acts in co-operation with the first osmotic composition for delivering the maximum amount of beneficial agent 15 from osmotic device 10. The second osmotic composition comprises an osmagent 18, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across wall 12 against an external fluid, blended with an osmopolymer 19 that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across wall 12 against external fluid. Osmopolymers 17 and 19 are hydrophilic water soluble or lightly cross-linked water insoluble polymers, and they possess osmotic properties such as the ability to imbibe external fluid, exhibit an osmotic pressure gradient across the semipermeable wall against the external fluid, and swell or expand in the presence of the fluid. Osmopolymers 17 and 19 are mixed with osmagent 16 and 18 for imbibing the maximum volume of external fluid into compartment 14. This fluid is available to osmopolymers 17 and 19 to optimize the volumetric rate and for total expansion of osmopolymers 17 and 19. That is, osmopolymers 17 and 19 absorb fluid imbibed into compartment 14 by the osmotic imbibition action of osmopolymers 17 and 19 supplemented by the osmotic imbibition action of osmagents 16 and 18 for effecting the maximum expansion of osmopolymers 17 and 19 to an enlarged state.

In operation, the delivery of beneficial agent 15 from osmotic device 10 is carried out, in one presently preferred embodiment, by (1) imbibition of fluid by the first composition to form a suspension in situ and delivery of the suspension through the passageway; and concurrently by (2) imbibition of fluid by the second composition causing the second composition to swell and co-operate with the first composition for driving the agent suspension through the passageway. According to the operation described, the osmotic device may be treated as a cylinder, with the second composition expanding like the movement of à piston for aiding in delivering the agent suspension from the osmotic device. Although the shape of the osmotic device as depicted in Figs. 1 and 2 is not a true cylinder, it is approximate enough for the following physical analysis. In this analysis, the volume rate delivered by the osmotic device F_t is composed of two sources; the water imbibition rate by the first composition F, and the water imbibition rate by the second composition Q wherein:

$$F_t = F + Q \qquad (1)$$

Since the boundary between the first composition and the second composition hydrates very

little during the functioning of the osmotic device, there is insignificant water migration between the compositions. Thus, the water imbibition rate of the second composition, Q, equals the expansion of its volume,

$$\frac{dv_p}{dt}=Q \quad (2)$$

The total delivery rate from the osmotic device is then,

$$\frac{dm}{dt}=F_t \cdot C=(F+Q)C \quad (3)$$

wherein C is the concentration of beneficial agent in the delivered slurry. Conservation of the osmotic device volume, V, and the surface area, A, gives equation 4 and 5:

$$V=V_d+V_p \quad (4)$$

$$A=A_d+V_p \quad (5)$$

wherein V_d and V_p equal the volumes of the first composition and the second composition respectively; and wherein A_d and A_p equal the surface area contact with the wall by the first composition and the second composition respectively. In operation, both V_p and A_p increase with time while V_d and A_d decrease with time as the device delivers beneficial agent.

The volume of the second composition that expands with time when fluid is imbibed into the compartment is given by equation 7:

$$V_p=\int\left(\frac{W_H}{W_p}\right) \quad (7)$$

wherein, W_H is the weight of fluid imbibed by the second composition, W_p is the weight of the second composition initially present in the device, W_H/W_p is the ratio of fluid to initial solid of the second composition, V_p equals

$$\left(1+\frac{W_H}{W_p}\right)\ \frac{W_p}{e}$$

wherein e is the density of the second composition corresponding to W_H/W_p. Thus, based on the geometry of a cylinder, where r is radius of the cylinder, the area of imbibition is related to the volume of the swollen second composition as follows:

$$A_p=r^2+\frac{2\,W_p}{r\ e}\ 1+\frac{W_H}{W_p} \quad (8)$$

$$A_d=A-A_p \quad (9)$$

The fluid imbibition rates into each compartment are:

$$F=\left(\frac{k}{h}\right)(A_d\,\Delta\pi_d) \quad (10)$$

$$Q=\left(\frac{k}{h}\right)(A_p\,\Delta\pi_p) \quad (11)$$

wherein k equals the osmotic permeability of the wall, h equals the wall thickness, $\Delta\pi_d$ and $\Delta\pi_p$ are the osmotic gradients for the first composition and the second composition respectively.

The total delivery rate, therefore, is:

$$\frac{dm}{dt} = \frac{k}{h} C A - \pi r^2 - \frac{2}{Y} \frac{W_p}{p} 1 + \frac{W_H}{W_p} \Delta\pi d + \pi p^2 + \frac{2}{r} \frac{W_p}{p} 1 + \frac{W_H}{W_p} \Delta\pi p \quad (12)$$

Figures 3 and 4 illustrate the osmotic device in operation as described for Figures 1 and 2. In Figures 3 and 4, for osmotic device 10, fluid is imbibed by the first composition at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall. The imbibed fluid continuously forms a solution containing beneficial agent, or a solution or of gel osmagent and osmopolymer containing beneficial agent in suspension, which solution or suspension in either operation is released by the combined operations of device 10. These operations include the solution, or the suspension being osmotically delivered through the passageway due to the continuous formation of solution or suspension, and by the swelling and increasing volume of the second composition, represented by the increase in height of the vertical lines in Figure 3 and 4. This latter swelling and increase in volume applies pressure against the solution or suspension thereby aiding the first composition and simultaneously causing delivery of beneficial agent to the exterior of the device.

The first composition and the second composition act together to substantially insure that delivery of beneficial agent from the compartment is constant over a prolonged period of time by two methods. *First,* the first composition imbibes external fluid across the wall, thereby forming either a solution or a suspension, the latter fraction of which would be substantially delivered at non-zero order (without the second composition present), since the driving force decays with time. *Second, the second composition* operates by two simultaneous operations: first, the second composition operates to continuously concentrate beneficial agent by imbibing some fluid from the first composition to help keep the concentration of beneficial agent from falling below saturation, and second, the second composition by imbibing external fluid across the wall continuously increases in volume, thereby exerting a force against the first composition and diminishing the volume of benefical agent, thusly directing beneficial agent to the passageway in the compartment. Additionally, since the extra solution or suspension formed in the first comparment is squeezed out, the osmotic composition cosely contacts the internal wall and generates a constant osmotic pressure, and therefore a constant delivery rate, in conjunction with the second composition. The swelling and expansion of the second composition, with its accompanying increase in volume, along with the simultaneous corresponding reduction in volume of the first composition, assures the delivery of beneficial agent at a controlled rate over time.

Device 10 of Figures 1 through 4 can be made into many embodiments including the presently preferred embodiments for oral use, for releasing either a locally or systemically acting therapeutic agent in a gastrointestinal tract. Oral system 10 can have various conventional shapes and sizes such as round with a diameter or 3/16 inches to 1/2 inch. In these forms, system 10 can be adapted for administering beneficial agent to numerous animals, including warm-blooded animals, humans, avains, reptiles and pisces.

Figures 5, 6 and 7 show another embodiment, an osmotic device 10 designed for placement in a body passageway, such as a vagina, or the ano-rectal canal. Device 10 has an elongated, cylindrical, self-sustaining shape with a rounded lead end 20, a trailing end 21, and it is equipped with manually controlled strings 22 for easily removing device 10 from a biological passageway. Device 10 is structurally identical with device 10 as described above and it operates in a like manner. In Figure 5, device 10 is depicted with a semi-permeable wall 23, in Figure 6 with a laminated wall 24 comprising an inner semi-permeable lamina 25 adjacent to compartment 14, and an external microporous lamina 26 distant from compartment 14. In Figure 7, device 10 comprises a laminated wall 28 formed of a microporous lamina 29 next to compartment 14, and a semi-permeable lamina 30 facing the environment of use and in laminar arrangement with microporous lamina 29. Device 10 delivers a beneficial agent for absorption by the vaginal mucosa, or the ano-rectal mucosa, to produce an in vivo local or systemic effect over a prolonged period of time.

The osmotic devices of Figures 1 through 7 can be used for delivering numerous agents including drugs at a controlled rate independent of the drug pH-dependency, or where the dissolution rate of the agent can vary between low and high in fluid environments, such as gastric fluid and intestinal fluid. The osmotic devices also provide for the high loading of agents of low solubility and their delivery at meaningful, therapeutic amounts. And, while Figures 1 through 7 are illustrative of various osmotic devices that can be made according to the invention, it is to be understood these devices are not to be construed as limiting, as the devices can take a wide variety of shapes, sizes and forms for delivering beneficial agents to the environment of use. For example, the devices include buccal, implant, artifical gland, cervical intrauterine, ear, nose, dermal, subcutaneous and blood delivery devices. The devices also can be sized, shaped, structured and adapted for delivering an active agent in streams, aquariums, field, factories, reservoirs, laboratory facilities, hot houses, transportation means, naval means, military means, hospitals, veterinary clinics, nursing homes, farms, zoos, sickrooms, chemical reactions, and other environments of use.

Detailed Description of the Invention

In accordance with the practice of this invention, it has now been found that osmotic delivery device 10 can be manufactured with a first osmotic composition and a second osmotic composition mutually housed in co-operative relationship in the compartment of the device. The compartment is formed by a wall comprising a material that does not adversely affect the beneficial agent, osmagent, osmopolymer and the like. The wall is permeable to the passage of an external fluid such as water and biological fluids, and it is substantially impermeable to the passage of agents, osmagents, osmopolymers, and the like. The wall is formed of a material that does not adversely affect an animal or a host, and the selectively semi-permeable materials used for forming the wall are non-erodible and they are insoluble in fluids. Typical materials for forming the wall are in one embodiment cellulose esters, cellulose ethers and cellulose ester-ethers. These cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di and tricellulose alkanylates, mono, di and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of 32 to 39.8; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%; and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioclanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioclanoate, cellulose dipentale, coesters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional semi-permeable polymers include ethyl cellulose, cellulose nitrate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate dimethyl aminoacetate, semi-permeable polyamides, semi-permeable polyurethanes, semi-permeable sulfonated polystyrenes, cross-linked selectively semi-permeable polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006; and 3,546,142; semi-permeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; lightly cross-linked polystyrene derivatives; cross-linked poly(sodium styrene sulfonate), cross-linked poly(vinylbenzyltrimethyl amonium chloride), semi-permeable polymers exhibiting a fluid permeability of 10^{-5} to 10^{-1} (cc.mil/cm^2.hr.atm) expressed per atmosphere 10^{-8} of hydrostatic or osmotic pressure difference across the semi-permeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971 published by CRC Press, Cleveland, Ohio.

The laminated wall comprising a semi-permeable lamina and a microporous lamina are in laminar arrangement and they act in concert to form an integral laminated wall, that maintains its physical and chemical integrity and does not separate into lamina through the operative agent release history of an osmotic device. The semi-permeable lamina is made from the semi-permeable polymeric materials presented above, the semi-permeable homopolymers, the semi-permeable copolymers and the like.

Microporous lamina suitable for manufacturing an osmotic device generally comprises performed microporous polymeric materials, and polymeric materials that can form a microporous lamina in the environment of use. The microporous materials in both embodiments are laminate to form the laminate wall. The preformed materials suitable for forming the microporous lamina are essentially inert, they maintain their physical and chemical integrity during the period of agent release and they can be generically described as having a sponge-like appearance that provides a supporting structure for a semi-permeable lamina and also provide a supporting structure for microscopic-sized interconnected pores or voids. The materials can be isotropic wherein the structure is homogenous throughout a cross-sectional area, or they can be anisotropic wherein the structure is non-homogenous throughout a cross-sectional area. The pores can be continuous pores that have an opening on both faces of a microporous lamina, pores interconnected through tortuous paths of regular and irregular shapes including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, microporous lamina are defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and the number of pores. The pore size of a microporous lamina is easily ascertained by measuring the observed pore diameter at the surface of the material under the electron microscope. Generally, materials possessing from 5% to 95% pores and having a pore size of from 10 angstroms to 100 microns can be used for making a microporous lamina. The pore size and other parameters characterizing the microporous structure also can be obtained from flow measurements, where a liquid

flux, J, is produced by a pressure difference ΔP, across the lamina. The liquid flux through a laminate with pores of uniform radius extended through the membrane and perpendicular to its surface with area A is given by relation 13:

$$J=\frac{N\pi^4\Delta P}{8\eta\Delta x} \qquad (13)$$

wherein J is the volume transported per unit time and lamina area containing N number of pores of radius r, η is the viscosity of the liquid, and ΔP is the pressure difference across the lamina with thickness Δx. For this type of lamina, the number of pores N can be calculated from relation 14, wherein ε is the porosity defined as the ratio of void volume to total volume of the lamina: and A is the cross-sectional area of the lamina containing N pores.

$$N=\frac{\varepsilon A}{\pi r^2} \qquad (14)$$

The pore radius then is calculated from relation 15:

$$r=8\eta\frac{\Delta x\,\tau}{\Delta p\,\varepsilon} \qquad (15)$$

wherein J is the volume flux through the lamina per unit area produced by the pressure difference ΔP across the lamina, η, ε and Δx have the meaning defined above and τ is the turtuosity defined as the ratio of the diffusional path length in the lamina to the lamina thickness. Relations of the above type are discussed in *Transport Phenomena In Membranes*, by Lakshiminatayanaiah, N, Chapter 6, 1969, published by Academic Press, Inc., New York.

As discussed in this reference on page 336, in Table 6.13, the porosity of the lamina having pores with radius r can be expressed relative to the size of the transported molecule having a radius a, and as the ratio of molecular radius to pore radius a/r decreases, the lamina becomes porous with respect to this molecule. That is, when the ratio a/r is less than 0.3, the lamina becomes substantially microporous as expressed by the osmotic reflection coefficient σ which decreases below 0.5. Microporous lamina with a reflection coefficient σ in the range of less than 1, usually from 0 to 0.5 and preferably less than 0.1 with respect to the active agent are suitable for fabricating the system. The reflection coefficient is determined by shaping the material in the form of a lamina and carrying out water flux measurements as a function of hydrostatic pressure difference and as a function of the osmotic pressure difference caused by the active agent. The osmotic pressure difference creates a hydrostatic volume flux, and the reflection coefficient is expressed by relation 16:

$$\sigma=\frac{\text{osmotic volume flux}}{\text{hydrostatic volume flux}} \qquad (16)$$

Properties of microporous materials are described in *Science,* Vol. 170 pages 1302 to 1305, 1970; *Nature,* Vol. 214 page 285, 1967; *Polymer Engineering and Science* Vol. 11 pages 284—288, 1971; U.S. Pat. Nos. 3,567,809 and 3,751,536; and in *Industrial Processing With Membranes* by Lacey R. E. and Loeb Sidney pages 131 to 134, 1972, published by Wiley, Interscience, New York.

Microporous materials having a preformed structure are commercially available and they can be made by art-known methods. The microporous materials can be made by etching, nuclear tracking, by cooling a solution of flowable polymer below the freezing point whereby solvent evaporates from the solution in the form of crystals dispersed in the polymer and then curing the polymer followed by removing the solvent crystals, by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a soluble component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte processes. Processes for preparing microporous materials are described in *Synthetic Polymer Membranes*, by R. E. Kesting, Chapters 4 and 5, 1971 published by McGraw Hill, Inc.; *Chemical Reviews,* Ultrafiltration, Vol. 18, pages 373 to 455, 1934; *Polymer Eng. and Sci.,* Vol. 11, No. 4, pages 284 to 288, 1971; *J. Appl. Poly Sci.,* Vol. 15, pages 811 to 829, 1971; and in U.S. Pat. Nos. 3,565,259; 3,615,024; 3,751,536; 3,801,692; 3,852,224 and 3,849,528.

Microporous materials useful for making the lamina include microporous polycarbonates comprises of linear polyesters of carbonic acid in which carbonate groups recur in the polymer chain, microporous materials prepared by the phosgenation of a dihydroxyl aromatic such as bisphenol A, microporous poly(vinylchloride), microporous polyamides such as polyhexamethylene adipamide, microporous modacrylic copolymers including those formed from poly(vinylchloride) 60% and

acrylonitrile, styrene-acrylic and its copolymers, porous polysulfones characterised by diphenylene sulfone groups in a linear chain thereof, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by exterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolic polyesters, microporous poly(saccharides), microporous poly(saccharides) having substituted and unsubstituted anhydroglucose units and preferably exhibiting an increased permeability to the passage of water and biological fluids than semi-permeable lamina, asymmetric porous polymers, cross-linked olefin polymers, hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and materials described in U.S. Pat. Nos. 3,597,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,061; 3,852,224; 3,853,601; and 3,852,388 in British Pat. No. 1,126,849 and in *Chem. Abst.,* Vol. 71 4274F, 22572F, 22573F, 1969.

Additional microporous materials include poly(urethanes), cross-linked, chain-extended poly(urethanes), microporous poly(urethanes) in U.S. Pat. No. 3,524,753 poly(imides), poly(benzimidazoles), collodion (cellulose nitrate with 11% nitrogen), regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols as in U.S. Pat. No. 3,565,259, anisotropic permeable microporous materials of ionically associated polyelectrolytes, porous polymers formed by the coprecipitation of a polycation and a polyanion as described in U.S. Pat. Nos. 3,276,589; 3,541,055; 3,541,066 and 3,546,142 derivatives of poly(styrene) such as poly(sodium styrenesulfonate) and poly(vinyl benzyltrimethyl-ammonium chloride), the microporous materials disclosed in U.S. Pat. No. 3,615,024 and U.S. Pat. Nos. 3,646,178 and 3,852,224.

Further, the microporous forming material used for the purpose of the invention, includes the embodiment wherein the microporous lamina is formed in situ, by a pore-former being removed by dissolving or leaching it to form the microporous lamina during the operation of the system. The pore-former can be a solid or a liquid. The term liquid, for this invention, embraces semi-solids and viscous fluids. The pore-formers can be inorganic or organic. The pore-formers suitable for the invention include pore-formers that can be extracted without any chemical change in the polymer. The pore-forming solids have a size of about 0.1 to 200 micrometres and they include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate and the like. The alkali earth metal salts include calcium phosphate, calcium nitrate and the like. The transition metal salts include ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, manganese fluoride, manganese fluorosilicate, and the like. The pore-formers include organic compounds such as polysaccharides. The polysaccharides include the sugars sucrose, glucose, fructose, mannitol, mannose, galactose, aldohexose, altrose, talose, sorbitol, lactose, monosaccharides and disaccharides. Also, organic aliphatic and aromatic oils and solids, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly(α-ω)-alkylenediols esters or alkylene glycols and the like; water soluble cellulosic polymers such as hydrosyloweralkyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, methylethyl cellulose, hydroxyethyl cellulose and the like; water soluble polymers such as polyvinylpyrrolidone, sodium carboxymethylcellulose and the like. The pore-formers are nontoxic and on their removal form the lamina channels are formed through the lamina. In a preferred embodiment, the nontoxic pore-forming agents are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly(α-ω)-alkylenediols, esters of alkylene glycols, glycols, and water soluble cellulosic polymers, useful for forming a microporous lamina in a biological environment. Generally, for the purpose of this invention, when the polymer forming the lamina contains more than 25% by weight of a pore-former, the polymer is a precursor microporous lamina that on removing the pore-former, yields a lamina which is substantially microporous, at concentrations less than this, the lamina behaves like a semi-permeable lamina or membrane.

The expression passageway as used comprises means and methods suitable for releasing the agent or drug from the osmotic system. The expression includes aperture, orifice, hole, or bore through the semi-permeable wall or the laminated wall. The passageway can be formed by mechanical drilling, laser drilling, or by eroding an erodible element, such as a gelatin plug, in the environment of use. A detailed description of osmotic passageways, and the maximum and minimum dimensions for a passageway are disclosed in United States Pat. Nos. 3,845,770 and 3,916,899.

The osmotically effective compounds that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across a semi-permeable wall, or across a semi-permeable microporous laminated wall, against an external fluid. The osmotically effective compounds (along with the osmopolymers) imbibe fluid into the osmotic device thereby making available in situ fluid for imbibition by an osmopolymer to enhance its expansion, and/or for forming a solution or suspension containing a beneficial agent for its delivery from the osmotic device. The osmotically effective compounds are known also as osmotically effective solutes, or osmagents. The osmotically effective compounds are used by mixing them with a beneficial agent and osmopolymer for forming a solution, or suspension containing the beneficial agent that is osmotically delivered from the device. The expression limited solubility as used herein means the agent has a solubility of about less than 5% by weight in the aqueous fluid present in the environment. The osmotic

solutes are used by homogenously or heterogenously mixing the solute with the agent or osmopolymer, and then charging them into the reservoir. The solutes and osmopolymers attract fluid into the reservoir producing a solution of solute in a gel which is delivered from the system concomitantly transporting undissolved and dissolved beneficial agent to the exterior of the system. Osmotically effective solutes used for the former purpose include magnesium sulfate, magnesium chloride, sodium chloride, potassium chloride, lithium chloride, potassium sulfate, sodium sulfate, lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, d-mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, α-d-lactose monohydrate, and mixtures thereof. The amount of osmagent in the compartment will generally be from 0.01% to 30%, or higher in the first composition, and usually from 0.01% to 40% or higher in the second compartment.

The osmotic solute is initially present in excess and it can be in any physical form that is compatible with the beneficial agent and the osmagent. The osmotic pressure of saturated solutions of various osmotically effective compounds and for mixtures of compounds at 37°C, in water, is listed in Table 1. In the table, the osmotic pressure π, is in atmospheres, ATM. The osmotic pressure is measured in a commercially available osmometer that measures the vapor pressure difference between pure water and the solution to be analyzed, and according to standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. In Table 1, osmotic pressures of from 20 ATM to 500 ATM are set forth; of course, the invention includes the use of lower osmotic pressures from zero, and higher osmotic pressures than those set forth by way of example in Table 1. The osmometer used for the present measurements is identified as Model 320B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard Co., Avonadale, Penna.

TABLE 1

Compound or Mixture	Osmotic Pressure ATM
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium Chloride	356
Fructose	355
Lactose-Sucrose	250
Potassium Chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Dextrose	82
Potassium Sulfate	39
Mannitol	38
Sodium Phosphate Tribasic · $12H_2O$	36
Sodium Phosphate Dibasic · $7H_2O$	31
Sodium Phosphate Dibasic · $12H_2O$	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic · H_2O	28

The osmopolyers suitable for forming the first osmotic composition, and also suitable forming the second osmotic composition are osmopolymers that exhibit fluid imbibition properties. The osmopolymers are swellable, hydrophilic polymers which interact with water and aqueous biological fluids and swell, or expand to an equilibrium state. The osmopolymers exhibit the ability to swell in water and retain a significant portion of the imbibed water within the polymer structure. The osmopolymers swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. The swellable, hydrophilic polymers are in one presently preferred embodiment lightly cross-linked, such cross-links being formed by covalent or ionic bonds. The osmopolymers can be of plant, animal, or synthetic origin. The osmopolymers are hydrophilic polymers. Hydrophilic polymers suitable for the present purpose include poly(hydroxyalkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; poly(vinylpyrrolidone) having a molecular weight of from 10,000 to 360,000; anionic and cationic hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) having a low acetate residual, cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization from 200 to 30,000; a mixture of methyl cellulose, cross-linked agar and carboxymethyl cellulose; a water-insoluble, water-swellable copolymer produced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene ethylene, propylene, butylene or isobutylene cross-linked with from 0.001 to about 0.5 moles of polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer; water-swellable polymers of N-vinyl lactams and the like.

Other osmopolymers include polymers that form hydrogels such as Carbopol acidic carboxy polymers having a molecular weight of 450,000 to 4,000,000; Cyanamer polyacrylamides; cross-linked water-swellable indene-maleic anhydride polymers; Good-rite polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox polyethylene oxide polymers having a molecular weight of 100,000 to 5,000,000; starch graft copolymers; Aqua-Keeps acrylate polymer; diester cross-linked polyglucan; and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Pat. No. 3,865,108 issued to Hartop; U.S. Pat. No. 4,002,173 issued to Manning; U.S. Pat. No. 4,207,893 issued to Michaels; and in *Handbook of Common Polymers* by Scott and Roff, published by the Chemical Rubber Co., Cleveland, Ohio. The amount of osmopolymer in the first osmotic composition is about .01 to 90% and the amount of osmopolymer in the second osmotic composition is 15 to 95%. In a presently preferred embodiment, the molecular weight of the osmopolymer in the second osmotic composition is larger than the molecular weight of the osmopolymer in the first osmotic composition.

Osmopolymer fluid imbibition determination for a chosen polymer can be made by following the procedure described below. A 1/2 inch round disc, fitted with a 1/2 inch diameter stainless steel plug, is charged with a known quantity of polymer with the plugs extending out either end. The plugs and the die were placed in a Carver press with plates between 200° and 300°F. A pressure of 10,000 to 15,000 PSI was applied to the plugs. After 10 to 20 minutes of heat and pressure, the electrical heating to the plates were turned off, and tap water circulated through the plates. The resulting 1/2 inch discs were placed in an air suspension coater charged with 1.8 kg saccharide cores and coated with cellulose acetate having an acetyl content of 39.8% dissolved in 94:6 w/w, CH_2Cl_2/CH_3OH, to yield a 3% w/w solution. The coated systems were dried overnight at 50°C the coated discs were immersed in water at 37°C and periodically removed for a gravimetric determination of water imbibed. The initial imbibition pressure was calculated by using the water transmission constant for the cellulose acetate, after normalizing imbibition values for membrane surface area and thickness. The polymer used in this determination was the sodium derivative of Carbopol-934 polymer, prepared according to the procedure of B. F. Goodrich Service Bulletin GC-36, "Carbopol Water-Soluble Resins", page 5, published by B. F. Goodrich, Akron, Ohio. The cumulative weight gain values, y, as a function of time, t, for the water soluble polymer disc coated with the cellulose acetate were used to determine the equation of the line $y=c+bt+at^2$ passing through those points by a least square fitting technique.

The weight gain for the Na Carbopol-934 is given by the equation 17 that follows: Weight Gain equals $0.359+0.665t-0.00106t^2$ wherein t is elapsed time in minutes. The rate of water flux at any time will be equal to the slope of the line, that is given by the following equation 18 and 19:

$$\frac{dy}{dt} = \frac{d(0.359+0.665t-0.00106t^2)}{dt} \qquad (18)$$

$$\frac{dy}{dt} = 0.665-0.00212t \qquad (19)$$

To determine the initial rate of water flux the derivative is evaluated at t=0, and dy/dt=0.665 μl/min, which is equal to the coefficient b. Then, normalizing the imbibition rate for time, membrane surface area and thickness, and the membrane permeability constant to water, K, π may be determined according to the following equation 20:

$$K\pi = 0.665\ \mu l/min \times \left(\frac{60\ min}{hr}\right) \times \left(\frac{1\ ml}{1000\ \mu l}\right)\left(\frac{0.008\ cm}{2.86\ cm^2}\right) \quad (20)$$

with $K=1.13\times10^{-4}$ cm²/hr. The (π) value for NaCl was determined with a Hewlett-Packard vapor pressure osmometer to be 345 atm±10%, and the K value for cellulose acetate used in this experiment calculated from NaCl imbibition values was determined to be 1.9×10^{-7} cm²/hr atm.

Substituting these values into the calculated Kπ expression (1.9×10^{-7}/cm²/hr.atm) (π)=1.13×10^{-4} cm²/hr gives π=600 atm at t=0. As a method for evaluating the efficiency of a polymer with respect to duration of zero-order driving force, the % of water uptake was selected before the water flux values decreased to 90% of their initial values. The value of the slope for the equation of a straight line emanating from the % weight gained axis will be equal to the initial value of dy/dt evaluated at t=0, with the y intercept c defining the linear swelling time, with (dy/dt) 0=0.665 and y intercept=0, which yields y=0.665t+0.359. In order to determine when the value of the cumulative water uptake is 90% below the initial rate, the following expression is solved for t,

$$0.9 = \frac{at^2+bt+c}{bt+c} = \frac{\Delta W}{w}0.9 \quad (21)$$

$$\frac{-0.00106t^2+0.665t+0.359}{0.665t+0.359} = 0.9, \text{ and} \quad (22)$$

solving for t,

$$-0.00106t^2+0.0665t+0.0359=0$$

$$t = \frac{-0.0665 \pm [(0.0665)^2-4(-0.00106)(0.0359)]^{1/2}}{2(-0.00106)} \quad (23)$$

t=62 min and the weight gain is $-0.00106(62)^2+(0.665)(62)+0.359=38\ \mu l$, with the initial sample weight=100 mg, thus (Δw/w) 0.9×100=38%. The results are presented in Figure 8 for a graphical representation of the values. Other methods available for studying the hydrogel solution interface include rheologic analysis, viscometric analysis, ellipsometry, contact angle measurements, electrokinetic determinations, infrared spectroscopy, optical microscopy, interface morphology and microscopic examination of an operative device.

The expression active agent as used herein, includes any beneficial agent, or beneficial compound, that can be delivered from the device to produce a benefical and useful result. The agent can be insoluble to very soluble in the exterior fluid that enters the device and it can be mixed with an osmotically effective compound and an osmopolymer. The term active agent includes pesticides, herbicides, germicides, biocides, algicides, rodenticides, fungicides, insecticides, antioxidants, plant growth, promoters, plant growth inhibitors, preservatives, disinfectants, sterilization agents, catalysts, chemical reactants, fermentation agents, sex sterilants, fertility inhibitors, fertility promoters, air purifiers, micro-organism attenuators, and other agents that benefit the environment of use.

In the specification and the accompanying claims, the term beneficial agent includes drug, and the term drug includes any physiologically or pharmacologically active substance that produces a local or systemic effect, in animals, including warm blooded mammals, humans and primates, avians, household, sport and farm animals, laboratory animals, fishes, reptiles and zoo animals. The term physiologically as used herein denotes the administration of a drug to produce normal levels and functions. The term pharmacologically denotes variations in response to amount of drug administered to the host. See *Stedman's Medical Dictionary*; 1966 published by Williams and Wilkins, Baltimore, Md. The phrase drug formulation as used herein means the drug is in the compartment mixed with an osmotic solute and/or an osmopolymer and if applicable, and with a binder and lubricant. The active drug that can be delivered includes inorganic and organic compounds without limitation, including drugs that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine system, hormone systems, immunological system, organ systems, reproductive system, skeletal system, autocoid systems, alimentary and excretory systems, inhibitory of autocoids and histamine systems. The active drug that can be delivered for acting on these animal systems includes depressants, hypnotics, sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesics, anti-inflammatory, local anesthetics, muscle contractants, anti-microbials, anti-malarials, hormonal agents, contraceptives, sympathomimetics, diuretics, anti-parasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, diagnostic agents and cardiovascular drugs.

Exemplary drugs that are very soluble in water and can be delivered by the devices of this

invention include prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproternol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, mechacholine chloride, pilocarpine hydrochloride, atropine sulfacte, methascopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol hydrochloride, metoprolol tartrate, imetidine hydrochloride, theophylline cholinate, cephalexin hydrochloride and the like.

Exemplary drugs that are poorly soluble in water and that can be delivered by the devices of this invention include diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythrityl tetranitrate, dizoxin, isofurophate, reserpine, acetazolamide, ethazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, profestins, esterogenic progestational, corticosteroids, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, triamcinolone, methyltesterone 17β-estradiol, ethinyl estradiol, prazosin hydrochloride ethinyl estradiol 3-methyl ether, pednisolone, 17β-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethiderone, progesterone, norgesterone, norethynodrel and the like.

Examples of other drugs that can be delivered by the osmotic device include aspirin, indomethacin, naproxen, fenoprofen, sulidac, diclofenac, indoprofen, nitroglycerin, propanolol, metoprolol, valproate, oxprenolol, timolol, atenolol, alprenolol, cimetidine, imipramine, levodopa, chloropromazine, reserpine, methyl-dopa, dihydroxyphenylalanine, pivaloyloxyethyl, ester of α-methyldopa hydrochloride, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, proszin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, α-blocking agents, calcium-channel blocking drugs such as nifedipine, diliazen, verapamil, betablockers and the like. The beneficial drugs are known to the art in *Pharmaceutical Sciences,* edited by Remington 14th Ed., 1979 published by Mack Publishing Co., Easton, Penna.; *The Drug, The Nurse, The Patient, Including Current Drug Handbook*, 1974—1976 by Falconer, et al., published by Saunder Company, Philadelphia, Penna.; and *Medicinal Chemistry,* 3rd Ed., Vol. 1 and 2 by Burger, published by Wiley-Interscience, New York.

The drug can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic drugs, salts of metals, amines or organic cations, for example quaternary ammonium, can be used. Derivatives of drugs such as esters, ethers and amides can be used. Also, a drug that is water insoluble can be used in a form that is a water soluble derivative thereof to serve as a solute and on its release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original biologically active form. The agent including drug, can be present in the compartment with a binder, dispersant, wetting agent, suspending agent, lubricant and dye. Representative of these include suspending agents such as acacia, agar, calcium carrageenan, alginic acid, algin, agarose powder, collagent, colloidal magnesium silicate, colloidal silicon dioxide, hydroxyethyl cellulose, pectin, gelatin and calcium silicate; binders like polyvinyl pyrrolidone, lubricants such as magnesium stearate, wetting agents such as fatty amines, fatty quaternary ammonium salts and the like. The phrase drug formulation indicates the drug is present in the compartment accompanied by an osmagent, osmopolymer, a binder and the like. The amount of beneficial agent in a device generally is about from 0.05 ng to 5 g or more, with individual devices containing for example, 25 ng, 1 mg, 5 mg, 125 mg, 250 mg, 500 mg, 750 mg, 1.5 g, and the like. The devices can be administered once, twice or thrice daily.

The solubility of a beneficial agent in the fluid can be determined by known techniques. One method consists of preparing a saturated solution comprising the fluid plus the agent as ascertained by analyzing the amount of agent present in a definite quantity of the fluid. A simple apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature and pressure, in which the fluid and agent are placed and stirred by a rotating glass spiral. After a given period of stirring, a weight of the fluid is analyzed and the stirring continued an additional period of time. If the analysis shows no increase of dissolved agent after successive period of stirring, in the presence of excess solid agent in the fluid, the solution is saturated and the results are taken as the solubility of the product in the fluid. If the agent is soluble, an added osmotically effective compound optionally may not be needed; if the agent has limited solubility in the fluid, then an osmotically effective compound can be incorporated into the device. Numerous other methods are available for the determination of the solubility of an agent in a fluid. Typical methods used for the measurement of solubility are chemical and electrical conductivity. Details of various methods for determining solubilities are described in United States *Public Health Service Bulletin,* No. 67 of the Hygenic Laboratory; *Encyclopedia of Science and Technology,* Vol. 12, pages 542 to 556, 1971, published by McGraw-Hill, Inc., and *Encyclopedia Dictionary of Physics,* Vol. 6, pages 547 to 557, 1962 published in Pergamon Press, Inc.

The osmotic devices of the invention is manufactured by standard techniques. For example, in

one embodiment, the beneficial agent is mixed with an osmagent and osmopolymer, and pressed into a solid possessing dimensions that correspond to the internal dimensions of the compartment adjacent to the passageway; or the beneficial agent and other formulation forming ingredients and a solvent are mixed into a solid or a semisolid by conventional methods such as ballmilling, calendering, stirring or rollmilling and then pressed into a preselected shape. Next, a layer of a composition comprising an osmagent and an osmopolymer is placed in contact with the layer of beneficial agent formulation, and the two layers surrounded with a semi-permeable wall. The layering of the beneficial agent composition and the osmagent/osmopolymer can be accomplished by conventional two-layer tablet press techniques. The wall can be applied by molding, spraying or dipping the pressed shaped into wall-forming material. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the pressed compositions in a current of air and a wall forming composition until the wall surrounds and coats the two pressed compositions. The procedure is repeated with a different lamina forming composition to form a laminated wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.,* Vol. 48, pages 451 to 459, 1979; and ibid, Vol. 49, pages 82 to 84, 1960. Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia,* Vol. 46, pages 62 to 70, 1969; and in *Pharmaceutical Sciences,* by Remington, 14th Edition, pages 1626 to 1678, 1970, published by Mack Publishing Co., Easton, Penna.

Exemplary solvents suitable for manufacturing the laminates and laminae include inert inorganic and organic solvents that do not adversely harm the materials and the final laminated wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water and mixtures thereof such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

Detailed Description of Examples

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An osmotic delivery device manufactured as an osmotic tablet shaped, sized and adapted for oral admittance into the gastrointestional tract is made as follows: a first osmotic drug composition is prepared by screening 355 g of poly(ethylene oxide) having an approximate molecular weight of 200,000 through a 40 mesh stainless steel screen, then 100 g of nifedipine is passed through the 40 mesh screen, 25 g of hydroxypropylmethylcellulose is passed through the 40 mesh screen, and finally 10 g of potassium chloride is passed through the 40 mesh screen. Next, all the screened ingredients are added to the blowl of a laboratory blender and the ingredients dry blended for 15—20 minutes to produce a homogeneous blend. Then a granulation fluid is prepared comprising 250 ml of ethanol and 250 ml of isopropyl alcohol and the granulating fluid added to the blending blowl; a first 50 ml is sprayed into the bowl with constant blending then 350 ml of the granulation fluid is added slowly to the bowl and the wet mass blended for another 15 to 20 minutes. Then the wet granules are passed through a 16 mesh screen and dried at room temperature for 24 hours, and the dry granules passed through a 16 mesh screen. Next, 10 g of magnesium stearate is added to the dry granules, and the ingredients roll-mixed for 20—30 minutes on a standard two roll mill.

Next, a second osmotic composition is prepared as follows: first, 170 g of poly(ethylene oxide) having a molecular weight of 5,000,000 is screened through a 40 mesh screen, then 72.5 g of sodium chloride is passed through the 40 mesh screen and the ingredients added to a mixing bowl and blended for 10—15 minutes. Then a granulation fluid is prepared by mixing 350 ml of methanol and 150 ml of isopropyl alcohol and the granulation fluid added to the blending bowl in two steps. First, 50 ml of the granulation fluid is sprayed into the bowl with constant blending, then 350 ml of the granulation fluid is slowly added to the bowl and the wet blend mixed for 15—20 minutes to a homogeneous blend. Then, the wet blend is passed through a 16 mesh screen, spread on a stainless steel tray and dried at room temperature of 22.5°C for 24 hours. The dried blend is passed through a 16 mesh screen, the roll milled with 5 g of magnesium stearate on a two roll mill for 20—30 minutes.

A number of drug cores are prepared by pressing the two compositions on Manesty Layerpress. The drug containing composition is fed into the cavity mold of the press and compressed into a solid

layer. Then, the second osmotic composition is fed into the cavity overlaying the compressed layer and pressed into a solid layer to form a two layered drug core.

The drug cores next are coated with a semi-permeable wall-forming composition comprising 95 g of cellulose acetate having an acetyl content of 39.8% and 5 g of poly(ethylene glycol) 4000 in a solvent comprising 1960 ml of methylene chloride and 820 ml of methanol. The drug cores are coated with the semi-permeable wall forming composition until the wall surrounds the drug core. A Wurster air suspension coater is used to form the semi-permeable wall. The coated cores are then spread on a tray and the solvent evaporated in a circulating air oven at 50°C for 65 hours. After cooling to room temperature a 0.26 mm diameter passageway is laser drilled through the semi-permeable wall connecting the exterior of the osmotic device with the composition containing the drug. The osmotic device weighed 262 mg and it contained 30 mg of drug in the first composition weighing 150 mg, the second composition weighed 75 mg and the semi-permeable wall weighed 37 mg. The first osmotic composition of the osmotic device comprises 30 mg of nifedipine, 106 mg of poly(ethylene oxide), 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate. The second osmotic composition comprises 51 mg of poly(ethylene oxide), 22 mg of sodium chloride, and 1.5 mg of magnesium stearate. The device has a diameter of 8 mm, a surface area of 1.8 cm^2 and the semi-permeable wall is 0.17 mm thick. The cumulative amount of drug released is depicted in Figure 9.

EXAMPLE 1A

Osmotic delivery systems are prepared having a first composition comprising 25 to 100 mg of nifedipine, 100 to 325 mg of poly(ethylene oxide) having a molecular weight of 200,000, 2 to 10 mg of potassium chloride, 5 to 30 mg of hydroxypropylmethylcellulose and 2 to 10 mg of magnesium stearate; and a second composition comprising 30 to 175 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 20 to 75 mg of sodium chloride and 1 to 5 mg of magnesium stearate. The procedure of Example 1 is repeated for preparing osmotic devices having the following compositions: (a) an osmotic device having a first composition comprising 60 mg of nifedipine, 212 mg of poly(ethylene oxide), 6 mg of potassium chloride, 15 mg of hydroxypropylmethylcellulose and 6 mg of magnesium stearate; and a second composition comprising 102 mg of poly(ethylene oxide), 44 mg of sodium chloride, and 3 mg of magnesium stearate; and (b) an osmotic device having a first composition comprising 90 mg of nifedipine, 318 mg of poly(ethylene oxide), 9 mg of potassium chloride, 22.5 mg of hydroxypropylmethylcellulose, and 9 mg of magnesium stearate, and a second composition comprising 102 mg of poly(ethylene oxide), 66 mg of sodium chloride, and 4.5 mg of magnesium stearate. In an embodiment, the osmotic device described in (a) and (b) further comprise a pulse coated on the outer semi-permeable wall. The pulse coat comprises 30 mg of nifedipine and hydroxypropylmethylcellulose. In operation in the fluid environment of use, the pulse coat provides instant drug availability for instant drug therapy.

EXAMPLE 2

The procedure of Example 1 is repeated with all conditions as previously described except that the drug in the compartment is replaced with a member from the group consisting of a beta-blocker, anti-inflammatory, analgesic, sympathomimetic, antiparkinson or a diuretic drug.

EXAMPLE 3

An osmotic therapeutic device for the controlled and the continuous oral release of the beneficial calcium channel blocker drug verapamil is made as follows: 90 mg of verapamil, 50 mg of sodium carboxyvinyl polymer having a molecular weight of 200,000 and sold under the trademark Carbopol® polymer, 3 mg of sodium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate are mixed thoroughly as described in Example 1, and pressed in a Manesty press with a 5/16 inch punch using a pressure head of 1-1/2 tons to produce a layer of the drug composition. Next, 51 mg of the carboxyvinyl polymer having a molecular weight of 3,000,000 and sold under the trademark Carbopol® polymer 22 mg of sodium chloride and 2 mg of magnesium stearate are blended thoroughly and added to the Manesty press, and pressed to form a layer of expandable, osmotic composition in contact with the layer of osmotic drug composition.

Next, a semi-permeable wall is formed by blending 170 g of cellulose acetate having an acetyl of 39.8% with 900 ml of methylene chloride and 400 ml of methanol and spray coating the two layered compartment forming member in an air suspension machine until a 5.1 mil thick semi-permeable wall surrounds the compartment. The coated device is dried for 72 hours at 50°C and then a 8 mil passageway is laser-drilled through the semi-permeable wall to connect the layer containing drug with the exterior of the device for releasing drug over a prolonged period of time.

EXAMPLE 4

The procedure of Example 3 is repeated with all conditions as described except that the drug in the osmotic device is fendiline, diazoxide, prenylamine or diltiazen.

EXAMPLE 5

An osmotic, therapeutic device for the delivering of the drug sodium diclofenac for uses as an anti-inflammatory is prepared by first pressing in a Manesty press an osmotic drug composition containing 75 mg of sodium diclofenac, 300 mg of sorbitol, 30 mg of sodium bicarbonate, 26 mg of pectin, 10 mg of polyvinyl pyrrolidone and 5 mg of stearic acid and pressing the composition in a cavity to a solid layer. Next, the cavity is charged with a second and greater force generating composition comprising 122 mg of pectin having a molecular weight of 90,000 to 130,000, 32 mg of mannitol, 20 mg of polyvinyl pyrrolidone and 2 mg of magnesium stearate and pressed to form a second layer in contacting relation with the first layer. The second layer had a density of 1.28 g/cm^3 and a hardness score of greater than 12 kg. Next, the two layer core is surrounded with a semi-permeable wall comprising 85 g of cellulose acetate having an acetyl content of 39.8%, and 15 g of polyethylene glycol 4000, 3 wt/wt % solid in a wall forming solvent comprising 1960 ml of methylene chloride and 819 ml of methanol. The coated device is dried for 72 hours at 50°C, and then a 0.26 mm diameter passageway is laser-drilled through the wall. The semi-permeable wall is 0.1 mm thick, the device has an area of 3.3 cm^2, and it has an average rate of drug release of 5.6 mg per hour over a 12 hour period. The cumulative amount released is illustrated in Figure 10. The small vertical bars represent the minimum and maximum drug release for five systems measured at that time.

EXAMPLE 5A

The procedure of Example 5 is followed for providing an osmotic device wherein the compartment contained a blend of osmopolymers. The compartment contained a first composition weighing 312 mg and consists of 48% sodium diclofenac drug, 38% poly(ethylene oxide) osmopolymer having a molecular weight of 200,000, 10% poly(ethylene glycol) osmopolymer having a molecular weight of 20,000, 2% sodium chloride, and 2% sodium chloride, and 2% magnesium stearate; and a second composition weighing 150 mg and consisting of 93% poly(ethylene oxide) having a molecular weight of 5,000,000, 5% sodium chloride, and 2% magnesium stearate.

EXAMPLE 6

In this example, the increase in osmotic pressure for a number of compositions comprising an osmagent and as osmopolymer are made for demonstrating the operative advantage provided by the invention. The measurements are made by measuring the amount of water imbibed across the semi-permeable wall of a bag containing as osmagent, or an osmopolymer, or a composition comprising an osmagent and an osmopolymer. The semi-permeable wall of the bag is formed of cellulose acetate having an acetyl content of 39.8%. The measurements are made by weighing the dry ingredients of the semi-permeable bag, followed by weighting the blotted semi-permeable bag, after the bag is in a water bath at 37°C for various lengths of time. The increase in weight is due to water imbibition across the semi-permeable wall caused by the osmotic pressure gradient across the wall. The osmotic pressure curves are illustrated in Figure 11. In Figure 11, the curved line with the triangles represents the osmotic pressure for poly(ethylene) oxide having a molecular weight of 5,000,000; the curved line with the circles represents the osmotic pressure for a composition comprising poly(ethylene) oxide having a molecular weight of 5,000,000 and sodium chloride with the ingredients present in the composition in the ratio of 9.5 parts osmopolymer to 0.5 parts osmagent; the curved line with squares represents a composition comprising the same osmopolymer and osmagent in the ratio of 9 parts osmopolymer to one part osmagent; the curved lines with hexagon represents the same composition comprising the osmopolymer and osmagent in the ratio of 8 parts to 2 parts; and the dashed lines represents the osmagent sodium chloride. The mathematical calculations are made using the formula $dw/dt=A(K\Delta\pi)/h$, wherein dw/dt is the rate of water imbibition over time, A is the area of the semi-permeable wall, and K is the permeability coefficient. Also, in Figure 11, W_H/W_p is the amount of water imbibed divided by the weight of osmopolymer plus osmagent.

EXAMPLE 7

An osmotic therapeutic device for dispensing sodium diclofenac is prepared by screening through a 40 mesh screen a composition comprising 49% of sodium diclofenac, 44% poly(ethylene) oxide having a molecular weight of 100,00, 2% sodium chloride and 3% hydroxypropylmethylcellulose, and then blending the screened composition with an alcohol solvent used in the ratio of 75 ml of solvent to 100 g of granulation. The wet granulation is screened through a 16 mesh screen, dried at room temperature for 48 hours under vacuum, passed through a 16 mesh screen and blended with 2% 80 mesh screened magnesium stearate. The composition is compressed as described above.

Next, a composition comprising 73.9% of pectin, having a molecular weight of 90,000 to 130,000, 5.8% microcrystalline cellulose, 5.8% polyvinyl pyrrolidone, 14.3% sodium chloride and 2% sucrose is passed through a 40 mesh screen, blended with an organic solvent in the ratio of 100 ml of solvent to 100 g of granulation for 25 minutes, passed through a 16 mesh screen, dried for 48 hours at room temperature under vacuum, again passed through a 16 mesh screen, blended with 2% magnesium stearate, and then compressed onto the compressed layer described in the above paragraph. The dual layered drug core is coated by dipping in a wall forming composition comprising

80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 4000, and 10% hydroxypropylmethylcellulose. A passageway is drilled through the wall communicating with the drug containing composition. The passageway diameter is 0.38 mm. The theoretical cumulative release profile for the device is depicted in Figure 12. Figure 13 depicts the theoretical release rate in mg per hour for the osmotic device.

EXAMPLE 8

The procedure of Example 7 is repeated with all conditions as described except that the osmopolymer in the drug composition is polyoxyethylene polyoxypropyleneblock copolymer having a molecular weight of about 12,500.

EXAMPLE 9

An osmotic device is made by following the above procedures. The device of this example comprises a single composition comprising 50% of sodium diclofenac, 46% of poly(ethylene) oxide having a molecular weight of 100,000, 2% sodium chloride and 2% magnesium stearate. The device has a semi-permeable wall comprising 90% cellulose acetate comprising 39.8% acetyl, and 10% polyethylene glycol 4000. The cumulative amount released for this device comprising the single composition is 40% of the device comprising two compositions. The cumulative amount released is illustrated in Figure 14.

EXAMPLE 10

The *in vivo* and *in vitro* mean cumulative releases of diclofenac sodium from an osmotic device comprising a first osmotic composition comprising 75 mg of diclofenac sodium 67 mg of poly(ethylene) oxide having a molecular weight of 100,000, 3.0 mg of sodium chloride, 4.5 mg of hydroxypropylmethylcellulose and 3.0 mg of magnesium stearate; a second osmotic composition distant from the releasing passageway comprising 51 mg of poly(ethylene) oxide having a molecular weight of 5,000,000, 22.5 mg of sodium chloride and 1.5 mg of magnesium stearate; and, surrounded by a semi-permeable wall comprising 90% cellulose acetate having an acetyl content of 39.8% and 10% polyethylene glycol 4000 was measured in vivo and in vitro in laboratory dogs. The amounts of drug released at various times in vivo were determined by administering a series of devices to the animal and measuring the amount released from the corresponding device at the appropriate residence time. The results are depicted in Figure 15, wherein the circles with the bars are the in vitro mean cumulative releases and the triangles with the bars are the in vivo mean cumulative releases.

The in vivo and in vitro mean cumulative release for a device containing nifedipine was measured as described immediately above. The osmotic device comprised a composition adjacent to the passageway comprising 30 mg of nifedipine, 106.5 mg of poly(ethylene) oxide having a molecular weight of 200,000, 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate; a composition distant form the passageway comprising 52 mg of poly(ethylene) oxide having a molecular weight of 5,000,000, 22 mg of sodium chloride and 1.5 mg of magnesium stearate; and a semi-permeable wall comprising 95% cellulose acetate having an acetyl content of 39.8% and 5% hydroxypropylmethylcellulose. Figure 16 depicts the release from the system. In Figure 16 the circles represent the in vivo cumulative release and the triangles represent the in vitro means cumulative release.

EXAMPLE 11

The procedure of Example 10 is followed for making an osmotic therapeutic delivery system comprising: a first or drug composition weighing 638 mg and consisting 96% cephalexin hydrochloride, 2% Poviclone (polyvinyl pyrrolidone) and 2% magnesium stearate; a second, or osmotic deriving composition weighing 200 mg and consisting of 68.5% poly(ethylene oxide) having a molecular weight of 5×10^6, 29.5% sodium chloride, and 2% magnesium stearate; a semi-permeable wall weighing 55.8 mg consisting of 80% cellulose acetate having an acetyl content of 39.8%, 14% polyethylene glycol 4000, and 14% hydroxypropylmethylcellulose; and an osmotic orifice having a diameter of 0.039 mm. The device has an average rate of release of about 54 mg per hour over a period of 9 hours.

The novel osmotic system of this invention uses dual means for the attainment of precise release rate of drugs that are difficult to deliver in the environment of use, while simultaneously maintaining the integrity and the character of the system. While there has been described and pointed out features and advantages of the invention as applied to the presently preferred embodiments, those skilled in the dispensing art will appreciate that various modifications, changes, additions and omissions in the system illustrated and described can be made without departing from the spirit of the invention.

CLAIMS

1. A device for the delivery at a controlled rate a beneficial agent to an environment of use, the device comprising:

a). a wall formed in at least a part of a composition permeable to the passage of an exterior fluid present in the environment of use, the wall surrounding and forming;

b). a compartment;

c). a first composition in the compartment, said first composition comprising a beneficial agent, an osmagent and an osmopolymer;

d). a second composition in the compartment, said second composition comprising an osmagent and an osmopolymer; and

e). a passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent from the device.

2. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the wall forming composition comprises a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, hydroxypropylmethylcellulose, hydroxyloweralkylcellulose, methylcellulose, methylethylcellulose and mixtures thereof.

3. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

4. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

5. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

6. The device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the beneficial agent is a drug.

7. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the wall is a laminate comprising a semi-permeable lamina and a microporous lamina.

8. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the composition forming the wall contains polyethylene glycol.

9. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the osmopolymer in the first composition is poly(ethylene oxide).

10. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the osmopolymer in the second composition is poly(ethylene oxide).

11. The device for the controlled delivery of the beneficial agent to the environment of use according to claim 1, wherein the agent is the drug nifedipine, verapamel, diltiazen, diclofenae, propanolol, proszin, ibuprofen, ketoprofen, haloperiodol, indomethacin, and cephalexin.

12. A device as claimed in claim 1 and substantially as herein described and/or with reference to the accompanying drawings.

13. Each and every novel embodiment herein set forth either separately or in combination.

New claims or amendments to claims filed on 3.7.84
Superseded claims 1—13
New or amended claims:—

1. A device for the delivery at a controlled rate a beneficial agent to an environment of use, the device comprising:

a) a wall formed in at least a part of a composition permeable to the passage of an exterior fluid present in the environment of use, the wall surrounding and forming;

b) a compartment;

c) a first composition in the compartment, said first composition comprising a beneficial agent and an osmopolymer;

d) a second composition in the compartment, said second composition comprising an osmagent and an osmopolymer; and

e) a passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent from the device.

2. The device for the delivery at a controlled rate the beneficial agent according to claim 2, wherein the wall forming composition comprises a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, hydroxypropylmethylcellulose, hydroxyloweralkylcellulose, methylcellulose, methylethylcellulose and mixtures thereof.

3. The device for the delivery at a controlled rate the beneficial agent according to either of claims 1 or 2, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

4. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

5. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

6. The device for the delivery at a controlled rate the beneficial agent according to any preceding claim, wherein the beneficial agent is a drug.

7. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the wall is a laminate comprising a semi-permeable lamina and a microporous lamina.

8. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the composition forming the wall contains polyethylene glycol.

9. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the osmopolymer in the first composition is poly(ethylene oxide).

10. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the osmopolymer in the second composition is poly(ethylene oxide).

11. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the agent is the drug nifedipine, verapamel, diltiazen, diclofenae, propanolol, proszin, ibuprofen, ketoprofen, haloperiodol, indomethacin, and cephalexin.

12. The device for the controlled delivery of the beneficial agent to the environment of use according to any preceding claim, wherein the first composition comprises an osmagent.

13. A device as claimed in claim 1 and substantially as herein described and/or with reference to the accompanying drawings.

14. Each and every novel embodiment herein set forth either separately or in combination.

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(54) Title: OSMOTIC MEDICAMENT RELEASING SYSTEM

(54) Bezeichnung: OSMOTISCHES ARZNEIMITTELFREISETZUNGSSYSTEM

(57) Abstract

The invention relates to an osmotic medicament releasing system which is to be administered orally, said system being comprised of a membrane and a dihydropyridine core, and to a method for the production of said releasing system. In addition, the invention relates to an osmotic medicament releasing system for use as medicaments for humans and animals and to the application of said osmotic medicament releasing system in order to produce a medicament to treat and/or prevent diseases in humans and animals.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft ein oral zu verabreichendes osmotisches Arzneimittelfreisetzungssystem, das aus einer Hülle und einem dihydropyridinhaltigen Kern besteht, sowie ein Verfahren zu dessen Herstellung. Die Erfindung betrifft weiter ein osmotisches Arzneimittelfreisetzungssystem zur Anwendung als Arzneimittel bei Menschen oder Tieren sowie die Verwendung des osmotischen Arzneimittelfreisetzungssystems zur Herstellung eines Arzneimittels zur Behandlung und/oder Prävention von Erkrankungen bei Menschen und Tieren.

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Osmotisches Arzneimittelfreisetzungssystem

Die vorliegende Erfindung betrifft ein oral zu verabreichendes osmotisches Arzneimittelfreisetzungssystem, das aus einer Hülle und einem wirkstoffhaltigen Kern besteht, sowie ein Verfahren zu dessen Herstellung. Die Erfindung betrifft weiter ein osmotisches Arzneimittelfreisetzungssystem zur Anwendung als Arzneimittel bei Menschen oder Tieren sowie die Verwendung des osmotischen Arzneimittelfreisetzungssystems zur Herstellung eines Arzneimittels zur Behandlung und/oder Prävention von Erkrankungen bei Menschen und Tieren.

Osmotische Arzneimittelfreisetzungssysteme sind grundsätzlich im Stand der Technik bekannt. Dabei wird im allgemeinen ein osmotischer Druck als Energiequelle ausgenutzt, einen Arzneimittelwirkstoff mit kontrollierter Geschwindigkeit an das umgebende Medium abzugeben. Daher nennt man solche Systeme auch osmotische Pumpen. Eine weitgehend vollständige Übersicht über die osmotischen Arzneimittelfreisetzungssysteme findet sich in Journal of Controlled Release 35 (1995) 1-21. Danach unterscheidet man prinzipiell zwischen Mehrkammersystemen und Einkammersystemen. Das Einkammersystem besteht in seiner einfachsten Form aus einer konventionellen Tablette, die aus der Hülle einer semipermeablen Membran mit einer Austrittsöffnung und einem Kern, in der der Wirkstoff in fester Form vorliegt, besteht. Nach der oralen Verabreichung dringt Wasser durch die semipermeable Membran in den Kern ein, der Wirkstoff löst sich auf und wird durch eine Austrittsöffnung abgegeben (US-Patent No. 3.845.770). Dieses Prinzip eignet sich jedoch nur für sehr gut wasserlösliche Wirkstoffe, da nur diese einen ausreichend hohen osmotischen Druck erzeugen können. Speziell für schwerlösliche Wirkstoffe wurden daher sogenannte Doppelkammersysteme („Push-Pull"-Systeme) entwickelt (US-Patent Nr. 4.111.202, Europäische Patentanmeldung Nr. 52 917). Die Herstellung solcher Zweikammersysteme ist jedoch technisch sehr aufwendig. Das Einkammersystem besitzt daher einen prinzipiellen Vorteil gegenüber den Mehrkammersystemen. Um die Vorteile des Einkammersystems bei schwerlöslichen Arzneimitteln dennoch zu nutzen, wurden zur Erzielung ausreichend hoher osmotischer Drücke im Innern der Tablette

Einkammersysteme vorgeschlagen, deren Kern aus dem Wirkstoff und bestimmten polymeren Quellmitteln besteht, die beim Hinzutreten von Wasser durch die äußere semipermeable Membran aufquellen und zusammen mit dem darin teilweise suspendierten Wirkstoff aus der Öffnung freigesetzt werden. Der Auswahl bestimmter polymerer Quellmittel kommt bei diesem System eine entscheidende Bedeutung zu, da wie in der EP-A-0 277 092 bereits beschrieben, bestimmte Quellmittel wie z.B. Polyvinylpyrrolidon, Polyethylenoxid oder Polymethacrylat einen so hohen Quelldruck erzeugen, daß es nach kurzer Zeit zu einer vollständigen Aufsprengung der semipermeablen Hüllmembran kommt und der Wirkstoff in kurzer Zeit freigesetzt wird, anstatt, wie gewünscht, verzögert bzw. kontrolliert freigesetzt zu werden. Die EP-A-0 277 092 trifft zur Lösung dieses Problems daher eine bestimmte Auswahl hydrophiler polymerer Quellmittel, nämlich eine Mischung aus einem Vinylpyrrolidon-Vinylacetat-Copolymer und einem Ethylenoxidhomopolymer.

Die WO 96/40080 beansprucht in generischer Form osmotische Einkammersysteme, die einen Kern aus einem pharmazeutischen Wirkstoff, einem wasserlöslichen osmotischen Mittel und einem wasserquellbaren Polymer umfassen. Wie jedoch bereits in der EP-A-0 277 092 dargelegt wird, sind nicht alle polymeren hydrophilen Quellmittel für diese Einkammersysteme geeignet, und eine sorgfältige Auswahl muß getroffen werden, um die gewünschte kontrollierte Freisetzung des Wirkstoffes aus dem Einkammersystem zu gewährleisten. In den konkreten Ausführungsformen der WO 96/40080 werden als wasserquellbare Polymere u.a. Polyethylenoxid und Cellulose bzw. deren Derivate verwendet.

Ein osmotisches Arzneimittelfreisetzungssystem mit kontrollierter, d.h. im allgemeinen mit verzögerter Freisetzung, das aus einem Einkammersystem besteht, sollte grundsätzlich eine möglichst vollständige Freisetzung des Wirkstoffes ermöglichen, ohne daß es während der Freisetzung zu einem Aufreißen der Austrittsöffnung und somit zu unkontrollierter Wirkstofffreisetzung kommt. Bei den Einkammersystemen besteht jedoch häufig das Problem, daß ein nicht unerheblicher Anteil des Wirkstoffs in der Tablette verbleibt, da der im Innern der Tablette erzeugte osmotische Druck nicht ausreicht, den Wirkstoff vollständig freizusetzen. So besitzen die oben beschriebenen

Systeme den Nachteil, daß sie den Wirkstoff nicht vollständig aus der Hüllmembran durch die Austrittsöffnung abgeben, so daß ein relativ hoher Anteil des Wirkstoffs nicht absorbiert wird und ungenutzt ausgeschieden wird. Wird jedoch auf der anderen Seite ein wasserquellbares Polymer verwendet, das einen sehr hohen osmotischen Druck erzeugt, kann dies zum Aufreißen oder gar zur vollständigen Sprengung der Tablette führen, so daß eine verzögerte, kontrollierte Freisetzung nicht erreicht wird.

Häufig weisen die osmotischen Arzneimittelfreisetzungssysteme des Stands der Technik auch das Problem auf, daß die unbeschichteten Tablettenkerne eine ungenügende mechanische Festigkeit aufweisen, was die nachfolgende Lackierung erschwert.

Grundsätzlich sollte ein osmotisches Arzneimittelfreisetzungssystem leicht herstellbar sein, aus preiswerten und pharmakologisch gut verträglichen Stoffen zusammengesetzt sein und es ermöglichen, ein günstiges Freisetzungsprofil des Wirkstoffs zu erreichen.

Es wurde nun überraschend gefunden, daß eine Kombination zweier bestimmter hydrophiler wasserquellbarer Polymere in bestimmten Gewichtsanteilen als Kernbestandteile besonders geeignet ist, die oben beschriebenen gewünschten Eigenschaften eines osmotischen Einkammer-Arzneimittelfreisetzungssystems, das einen pharmazeutischen Wirkstoff, insbesondere ein Dihydropyridin umfaßt, zu erreichen. Die Erfinder der vorliegenden Erfindung fanden, daß die Kombination aus dem Heteropolysaccharid Xanthan und einem Vinylpyrrolidon-Vinylacetat-Copolymer als wasserquellbare Polymere in bestimmten Gewichtsmengen zu einer weitgehend vollständigen Freisetzung eines Wirkstoffes aus der Hülle führt, ohne daß es dabei zu einem Aufreißen der Öffnung und unkontrollierter Wirkstofffreisetzung kommt.

Ohne an eine Theorie gebunden zu sein, wird angenommen, daß das Xanthan in Kombination mit dem Vinylpyrrolidon-Vinylacetat-Copolymer insbesondere deshalb sehr günstige Freisetzungseigenschaften bewirkt, da es strukturviskose Lösungen bildet, deren Viskosität beim Fließen unter dem Einfluß zunehmender Schubspannung

abnimmt. Dies erlaubt offenbar eine besonders gleichförmige Freisetzung des Wirkstoffs aus der Austrittsöffnung, ohne daß es zum Einreißen der Membran kommt, und dabei wird der Wirkstoff über einen relativ langen Zeitraum gleichförmig und weitgehend vollständig freigesetzt.

Xanthan als wasserquellbares Polymer besitzt darüberhinaus gegenüber den in der EP-A-0 277 092 und der WO 96/40080 verwendeten Polyethylenoxiden den Vorteil der leichteren Handhabbarkeit, da es nicht den sogenannten TOMS-Effekt (Herabsetzung des Reibungswiderstands) aufweist. Ein weiterer Vorteil der Verwendung des Xanthans gegenüber der Verwendung von Polyethylenoxiden als wasserquellbare Polymere besteht darin, daß Polyethylenoxide in der Regel nur mit organischen Lösungsmitteln feucht granuliert werden (s. z.B. Beispiele der EP-A-0 277 092), so daß die Herstellung unter Explosionsschutz erfolgen muß, oder es wird trocken tablettiert (WO 96/40080), so daß die bekannten Nachteile der Trockentablettierung, wie schlechte Fließfähigkeit der Mischung der Kernbestandteile, Staubentwicklung sowie eine geringere Härte des Tablettenkerns auftreten.

Die vorliegende Erfindung überkommt die oben beschriebenen Probleme des Stands der Technik mit der Bereitstellung eines osmotischen Arzneimittelfreisetzungssystem, daß besteht aus:

- einer Hülle aus einem wasserdurchlässigen, für die Komponenten des Kerns undurchlässigen Material, die mindestens eine Öffnung aufweist, und

- einem Kern, enthaltend

  - 15 bis 35 Gew.-% eines pharmazeutischen Wirkstoffs
  - 20 bis 50 Gew.-% Xanthan
  - 10 bis 30 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydro-

philen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100 % aufaddiert.

Die Hülle des osmotischen Arzneimittelfreisetzungssystems besteht aus einem wasserdurchlässigen, für die Komponenten des Kerns undurchlässigen Material. Solche Hüllmaterialien sind im Prinzip bekannt und beispielsweise beschrieben in der EP-A-0 277 092. Zur Herstellung der Hülle eignen sich z.B. die literaturbekannten polymeren Stoffe, die im Gastrointestinaltrakt nicht metabolisiert werden, d.h. unverändert ausgeschieden werden (s. US-Patente Nr. 3.916.899 und Nr. 3.977.404). Beispielsweise können acylierte Cellulosederivate (Celluloseester), die durch Acetylgruppen ein- bis dreifach oder durch Acetylgruppen ein- bis zweifach und einen weiteren von Acetyl verschiedenen Acylrest substituiert sind, verwendet werden, z.B. Celluloseacetat, Cellulosetriacetat, Celluloseacetatethylcarbamat, Celluloseacetatphthalat, Celluloseacetatmethylcarbamat, Celluloseacetatsuccinat, Celluloseacetatdimethylaminoacetat, Celluloseacetatethylcarbonat, Celluloseacetat-chloracetat, Celluloseacetatethyloxalat, Celluloseacetat-methylsulfonat, Cellulose-acetatbutylsulfonat, Celluseacetatpropionat, Celluloseacetatdiethylaminoacetat, Celluloseacetatoctat, Celluloseacetatlaurat, Celluloseacetat-p-toluolsulfonat, Cellu-loseacetatbutyrat und andere Celluloseacetatderivate sowie Agaracetat und Amy-loseacetat. Als semipermeables Membranmaterial eignen sich auch Ethylcellulose und polymere Epoxide, Copolymere aus Alkylenoxid und Alkylglycidylethern, Polyglykole und Polymilchsäurederivate und weitere Derivate davon. Ferner können auch Mischungen von an sich wasserunlöslichen Acrylaten (z.B. ein Copolymerisat von Acrylsäureethylester und Methacrylsäuremethylester) verwendet werden. Auf die Hülle kann bei Bedarf ein Lichtschutzlack aufgebracht werden. Geeignete Materialien für den Lichtschutzlack sind z.B. Polymere, wie Hydroxypropylcellulose, Hydroxypropylmethylcellulose, in Kombination mit geeigneten Weichmachern wie z.B. Polyethylenglykol und Pigmenten wie z.B. Titandioxid oder Eisenoxide.

Die Mengen und die verwendeten Bestandteile für die Herstellung der Hülle des osmotischen Arzneimittelfreisetzungssystems beeinflussen in bekannter Weise die Eintrittsgeschwindigkeit der gastrointestinalen Flüssigkeit. Grundsätzlich nimmt die Eintrittsgeschwindigkeit der gastrointestinalen Flüssigkeit mit zunehmender Lackmenge ab.

Die Hülle des osmotischen Arzneimittelfreisetzungssystems der vorliegenden Erfindung weist mindestens eine Öffnung bzw. Passage auf, durch die der Wirkstoff zusammen mit den weiteren Kernbestandteilen allmählich austritt. Die Öffnung wird durch Laserbohren, mechanisches Bohren oder z.B. Stanzen in die Hülle eingebracht. Es können ein oder mehrere Öffnungen in der Hülle vorhanden sein. Die Größe der Öffnung beträgt bevorzugt 0,2 bis 1,6 mm, besonders bevorzugt 0,4 bis 1,2 mm. Die Beschaffenheit und die Herstellverfahren der Öffnung sind an sich bekannt und beispielsweise beschrieben in den US-Patenten Nr. 4063064, 4088864 und 3916899 sowie in der EP-B-0277092.

Der Kern des osmotischen Arzneimittelfreisetzungssystems der vorliegenden Erfindung enthält, bzw. besteht im wesentlichen aus den folgenden Bestandteilen:

- 15 bis 35 Gew.-% eines pharmazeutischen Wirkstoffs
- 20 bis 50 Gew.-% Xanthan
- 10 bis 30 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

Bevorzugt besteht der Kern aus:

- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
- 25 bis 40 Gew.-% Xanthan
- 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

Weitere auf dem Gebiet der osmotischen Arzneimittelfreisetzungssysteme übliche Bestandteile können enthalten sein, solange ihre Anwesenheit, die Lösung der eingangs beschriebenen Aufgabenstellung nicht beeinträchtigt.

Bei den im Kern befindlichen pharmazeutischen Wirkstoffen handelt es sich vorzugsweise um schwerlösliche Wirkstoffe mit einer maximalen Löslichkeit von $\leq$ 1 g in 1000 g Wasser, vor allem um solche, die auch noch im Dickdarm resorbiert werden, insbesondere um einen Wirkstoff der an sich bekannten Klasse der Dihydropyridine, wie sie zum Beispiel in der EP-A-0071819 beschrieben sind, z.B. Nifedipin und Nisoldipin. Sie wirken als Calciumantagonisten. Diese werden sowohl als Herzkreislaufmittel in der Indikation Bluhochdruck als auch in der Behandlung und Prävention ischämischer Gehirnerkrankungen eingesetzt.

Besonders bevorzugt wird Nifedipin verwendet.

Der Wirkstoff liegt im Kern des osmotischen Arzneimittelfreisetzungssystem der vorliegenden Erfindung in einer Menge von 15 bis 35 Gew.-%, bevorzugt 20 bis 30 Gew.-%, besonders bevorzugt 19 bis 23 Gew.-%, bezogen auf die Gesamtmenge der Kernbestandteile vor.

Das osmotische Arzneimittelfreisetzungssystem enthält als einen der wesentlichen Bestandteil des Kerns das hydrophile wasserquellbare Polymer Xanthan. Dabei handelt es sich um ein anionisches Heteropolysaccharid, das im Handel beispielsweise unter der Bezeichnung Rhodigel® (hergestellt durch Meyhall) erhältlich ist.

In einer bevorzugten Ausführungsform weist das Xanthan eine Partikelgröße von weniger als 800 µm auf. Eine Partikelgröße von mehr als 800 µm führt in einigen Fällen zu einem verschlechterten Freisetzungsverhalten. In einer besonders bevorzugten Ausführungsform beträgt die Partikelgröße des Xanthans weniger als 500 µm.

Das Xanthan liegt in einer Menge 20 bis 50 Gew.-%, bevorzugt 25 bis 40 Gew.-% besonders bevorzugt 28 bis 32 Gew.-%, bezogen auf die Gesamtmenge der Kernbestandteile vor.

Ein weiterer wesentlicher Bestandteil des Kerns des Arzneimittelfreisetzungssystems der vorliegenden Erfindung ist das Vinylpyrrolidon-Vinylacetat-Copolymer. Dieses Copolymer ist an sich bekannt und kann mit beliebigen Mischungsverhältnissen der Monomere hergestellt werden. Das bevorzugt verwendete kommerziell erhältliche Kollidon® VA64 (hergestellt durch BASF) ist z.B. ein 60:40- Copolymerisat. Es weist im allgemeinen einen Gewichtsmittelwert des Molekulargewichts Mw, bestimmt durch Lichtstreuungsmessungen, von etwa 45.000 bis etwa 70.000 auf. Die Menge des Vinylpyrrolidon-Vinylacetat-Copolymers im Kern des Arzneimittelfreisetzungssystems der vorliegenden Erfindung beträgt 10 bis 30 Gew.-%, bevorzugt 10 bis 20 Gew.-%, besonders bevorzugt 15 bis 20 Gew.-%, bezogen auf das Gesamtgewicht der Kernbestandteile. Daraus ergibt sich ein bevorzugtes Gewichtsverhältnis von Xanthan zum Vinylpyrrolidon-Vinylacetat-Copolymer von 5 : 1 bis 2 : 3.

Bevorzugt enthält das osmotische Arzneimittelfreisetzungssystem der vorliegenden Erfindung lediglich Xanthan und das Vinylpyrrolidon-Vinylacetat-Copolymer als wasserquellbare Polymere als Kernbestandteile.

In einer besonders bevorzugten Ausführungsform der Erfindung enthält das osmotische Arzneimittelfreisetzungssystem mindestens einen osmotisch aktiven Zusatz und/oder mindestens einen pharmazeutisch annehmbaren Zusatzstoff.

Dabei ist ein osmotisches Arzneimittelfreisetzungssystem bevorzugt, dessen Kern enthält:

- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
- 25 bis 40 Gew.-% Xanthan
- 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
- 10 bis 30 Gew.-% einer osmotisch aktiven Substanz,
- 8 bis 20 Gew.-% mindestens eines pharmazeutisch annehmbaren Zusatzstoffes,

wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

Obwohl es bevorzugt ist, daß das osmotische Arzneimittelfreisetzungssystem der vorliegenden Erfindung lediglich Xanthan und das Vinylpyrrolidon-Vinylacetat-Copolymer als wasserquellbare Polymere als Kernbestandteile enthält, können bei Bedarf weitere zusätzliche hydrophile quellbare Polymere im Kern enthalten sein, die z.B. ausgewählt werden aus Hydroxypropylcellulose, Hydroxypropyl-methylcellulose, Natriumcarboxymethylcellulose, Polyacrylsäuren bzw. deren Salze.

Die gegebenenfalls im Kern vorhandenen weiteren hydrophilen quellbaren Polymere liegen im Arzneimittelfreisetzungssystem der vorliegenden Erfindung in einer Menge vor, bei der die Lösung der eingangs beschriebenen Aufgabenstellung nicht beeinträchtigt ist.

Diese hydrophilen wasserquellbaren Polymere, die in der vorliegenden Erfindung verwendet werden, umfassen jedoch kein Polyethylenoxid (Polyethylenglykol), d.h. der Kern der Arzneimittelfreizusammensetzung der vorliegenden Erfindung ist frei von Polyethylenoxidzusätzen.

Die wahlweise im Kern des Arzneimittelfreisetzungssystems der vorliegenden Erfindung enthaltenen osmotisch aktiven Zusätze sind im Prinzip nicht beschränkt, und alle wasserlöslichen Stoffe, deren Verwendung in der Pharmazie unbedenklich ist, wie z.B. die in Pharmakopöen oder in „Hager" und „Remington Pharmaceutical Science" erwähnten wasserlöslichen Hilfsstoffe können verwendet werden. Insbesondere können wasserlösliche Salze von anorganischen oder organischen Säuren oder nichtionische organische Stoffe mit großer Wasserlöslichkeit wie z.B. Kohlehydrate, insbesondere Zucker, oder Aminosäuren verwendet werden. Zum Beispiel können die osmotisch aktiven Zusätze ausgewählt werden aus anorganischen Salzen wie Chloriden, Sulfaten, Carbonaten und Bicarbonaten von Alkali- oder Erdalkalimetallen, wie Lithium, Natrium, Kalium, Magnesium, Calcium sowie Phosphate, Hydrogen- oder Dihydrogenphosphate, Acetate, Succinate, Benzoate, Citrate oder Ascorbate davon. Des weiteren können Pentosen, wie Arabinose, Ribose oder Xylose, Hexosen, wie Glucose, Fructose, Galactose oder Mannose, Disaccharide wie Sucrose, Maltose oder Lactose oder Trisaccharide wie Raffinose verwendet werden. Zu den wasserlöslichen Aminosäuren zählen Glycin, Leucin, Alanin oder Methionin. Besonders bevorzugt wird Natriumchlorid verwendet. Diese osmotisch aktiven Zusätze sind bevorzugt in einer Menge von 10 bis 30 Gew.-%, besonders bevorzugt 15 bis 20 Gew.-%, bezogen auf die Gesamtmenge der kernbildenden Bestandteile enthalten.

Desweiteren kann der Kern des osmotischen Arzneimittelfreisetzungssystems der vorliegenden Erfindung einen oder mehrere pharmazeutisch annehmbare Zusatzstoffe enthalten, die ausgewählt werden aus: Pufferstoffen, wie z.B. Natriumbicarbonat, Sprengmitteln, wie z.B. Natriumcarboxymethylstärke, Gleitmitteln, wie z.B. Magnesiumstearat, Tablettierhilfsmitteln, Schutzkolloiden, wie z.B. in der EP-B-0277092, S. 5, Z. 10-25 beschrieben, Weichmachern, wie z.B. in der EP-B-0277092, S. 5, Z. 29-32 beschrieben, Tensiden, wie z.B. in der EP-B-0277092, S. 5, Z. 33-44 beschrieben, Trägermaterialien, wie z.B. in der EP-B-0277092, S. 5, Z. 45-47 beschrieben.

In einer ganz besonders bevorzugten Ausführungsform der vorliegenden Erfindung umfaßt der Kern:

- 19 bis 23 Gew.-% eines pharmazeutischen Wirkstoffs
- 28 bis 32 Gew.-% Xanthan
- 15 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
- 15 bis 20 Gew.-% Natriumchlorid
- 5 bis 7 Gew.-% Natriumbicarbonat
- 6 bis 9 Gew.-% Natriumcarboxymethylstärke
- <1 Gew.-% Magnesiumstearat

wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

Das osmotische Arzneimittelfreisetzungssystems der vorliegenden Erfindung kann in verschiedenen Formen wie z.B. in der EP-B-0277092, S. 6, Z. 7-14 beschrieben vorliegen. Bevorzugt liegt es in Tablettenform vor.

Die Erfindung betrifft auch ein Verfahren zur Herstellung des erfindungsgemäßen osmotischen Arzneimittelfreisetzungssystems, bei dem die Bestandteile des Kerns miteinander vermischt werden, gegebenenfalls feucht oder trocken granuliert werden, tablettiert werden und der so entstandene Kern mit der Hülle beschichtet wird. Die Feuchtgranulation bewirkt häufig eine bessere Benetzbarkeit der Bestandteile des Tablettenkerns, wodurch die eintretende Gastrointestinalflüssigkeit den Kern besser durchdringt, was vielfach zu einer rascheren und vollständigeren Freisetzung des Wirkstoffs führt, so daß die Feuchtgranulation bevorzugt ist.

Das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem wird zur Behandlung und/oder Prävention von Erkrankungen von Menschen und Tieren, wie z.B. bei Kreislauferkrankungen, Infektionen, Entzündungen, Schmerzzuständen, Asthma, Cancer, Malaria, Thrombosen, Diabetes, Herzrhythmusstörungen, Hypoglycaemien, Mycosen, Depressionen, Störungen des Salz- und Flüssigkeitshaushaltes, Stoff-

wechselstörungen wie z.B. Störungen des Fettstoffwechsels, koronaren Herzerkrankungen, Bluthochdruck, cerebralen Leistungsstörungen und zur Therapie neurologischer Defizite insbesondere nach Subarachnoidalblutung verwendet. Besonders bevorzugt werden die osmotischen Arzneimittelfreisetzungssysteme der vorliegenden Erfindung zur Behandlung von Bluthochdruck und koronaren Herzerkrankungen verwendet.

Beispiel 1 und 2 (Tabletten mit trocken granulierten Bestandteilen)

Zusammensetzung

Kern

	1	2
Nifedipin	36,00 mg	36,00 mg
Xanthan (Rhodigel®, Handelsprodukt, Meyhall)	50,96 mg	50,96 mg
Copolyvidon (Kollidon® VA64, Handelsprodukt, BASF, Vinylpyrrolidon-Vinylacetat-Copolymer)	29,45 mg	29,45 mg
Natriumchlorid	28,71 mg	28,71 mg
Natriumbicarbonat	10,15 mg	10,15 mg
Natriumcarboxymethylstärke	12,74 mg	12,74 mg
Aerosil	0,85 mg	0,85 mg
Mg-stearat	0,68 mg	0,68 mg

Hülle (osmotische Membran)

Celluloseacetat	8,45 mg	11,40 mg
Polyethylenglykol 3350	0,45 mg	0,60 mg
Tbl.-gewicht ca.	178,5 mg	181,6 mg
Tbl-format	6r9	6r9

Herstellungsverfahren

Nifedipin, Kollidon® VA64 (70 Gew.% der o.a. Menge), Rhodigel® Natriumchlorid und Natriumbicarbonat wurden gemischt und anschließend trocken granuliert. Das Granulat wurde mit Natriumcarboxymethylstärke, dem anteiligen Rest von Kollidon® VA64, Aerosil und Magnesiumstearat nachgemischt. Die Mischung wurde anschließend tablettiert. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Die beschichteten Tabletten wurden anschließend getrocknet. Die enstandenen Tabletten besaßen einen Durchmesser von 6 mm.

Anschließend wurde eine Öffnung von ca. 800 µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht.

Beispiel 3 und 4 (Tabletten mit feucht granulierten Bestandteilen)

Zusammensetzung

Kern

	3	4
Nifedipin	36,00 mg	36,00 mg
Xanthan (Rhodigel®, Handelsprodukt, Meyhall)	50,96 mg	50,96 mg
Copolyvidon (Kollidon® VA64, Handelsprodukt, BASF, Vinylpyrrolidon-Vinylacetat-Copolymer)	29,45 mg	29,45 mg
Natriumchlorid	28,71 mg	28,71 mg
Natriumbicarbonat	10,15 mg	10,15 mg
Natriumcarboxymethylstärke	12,74 mg	12,74 mg
Aerosil	0,90 mg	0,90 mg
Mg-stearat	0,50 mg	0,50 mg

Hülle (osmotische Membran)

Celluloseacetat	7,50 mg	9,40 mg
Polyethylenglykol 3350	0,40 mg	0,50 mg
Tbl.-gewicht ca.	177 mg	179 mg
Tbl-format	6r9	7r10

Herstellungsverfahren

Rhodigel®, Natriumchlorid, Natriumbicarbonat und Natriumcarboxymethylstärke wurden gemischt und anschließend mit einer Suspension von Nifedipin und Kollidon® VA64 in Wasser feucht granuliert. Das Granulat wurde mit Aerosil und Magnesiumstearat nachgemischt. Die Mischung wurde anschließend tablettiert. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Die beschichteten Tabletten wurden anschließend getrocknet. Die enstandenen Tabletten besaßen einen Durchmesser von 6 mm bzw. 7 mm.

Anschließend wurden zwei Öffnungen von je ca. 600µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht.

Vergleichsbeispiel 1 (entsprechend Beispiel 3 der EP-A-0277092):

Zusammensetzung

Kern

Nifedipin	50,00 mg
Polyox coagulant	20,00 mg
Copolyvidon (Kollidon® VA64, Handelsprodukt, BASF, Vinylpyrrolidon-Vinylacetat-Copolymer)	18,00 mg
Natriumchlorid	20,00 mg
Mg-stearat	2,00 mg

Hülle (osmotische Membran)

Celluloseacetat	11,20 mg
Polyethylenglykol 4000	1,50 mg
Tbl.-gewicht ca.	122,7 mg
Tbl-format	7r10

Herstellungsverfahren

Nifedipin, Polyox coagulant, Kollidon® VA64, Natriumchlorid und Magnesiumstearat wurden gemischt. Die Mischung wurde anschließend jedoch zur Vermeidung der Verwendung organischer Lösungsmittel ohne vorherige Granulation direkt tablettiert. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Es wurde dabei Celluloseacetat Typ 398-10 anstatt Celluloseacetat Typ 320S eingesetzt, um die Verwendung von chlorierten Kohlenwasserstoffen zu vermeiden. Die beschichteten Tabletten wurden anschließend getrocknet. Die enstandenen Tabletten besaßen einen Durchmesser von 7 mm.

Anschließend wurde eine Öffnung von ca. 800 µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht.

Vergleichsbeispiel 2 (entsprechend Beispiel 1 der WO-96/40080):

Zusammensetzung

Kern

Nifedipin	33,00 mg
Polyox WSR 303	27,50 mg
Polyox WSR N80	55,00 mg
Natriumcarboxymethylstärke	82,50 mg
Lactose	74,25 mg
Mg-stearat	2,75 mg

Hülle (osmotische Membran)

Celluloseacetat	12,48 mg
Polyethylenglykol 400	0,78 mg
Saccharose micr.	1,56 mg
Triacetin	0,78 mg

Tbl.-gewicht ca.	291 mg
Tbl-format	9r15

Herstellungsverfahren

Nifedipin, Polyox WSR 303, Polyox WSR N80, Natriumcarboxymethylstärke, Lactose und Magnesiumstearat wurden gemischt. Die Mischung wurde anschließend tablettiert. Die entstandenen Tablettenkerne waren sehr weich und ließen sich nur schlecht weiterverarbeiten. Die Tablettenkerne wurden mit einem die Bestandteile der osmotischen Membran enthaltenden organischen Lack beschichtet. Die beschichteten Tabletten wurden anschließend getrocknet. Die enstandenen Tabletten besaßen einen Durchmesser von 9 mm. Anschließend wurde eine Öffnung von ca. 800 µm im Durchmesser bei jeder Tablette mit einem Handbohrer angebracht. Die in Figur 1 der WO-96/40080 gezeigten Freisetzungsmengen des Beispiels 1 der WO-96/40080 wurden unter den unten angegebenen Testbedingungen nicht gefunden.

Die in den Beispielen und Vergleichsbeispielen hergestellten osmotischen Arzneimittelfreisetzungssysteme wurden auf ihr Freisetzungsverhalten in der „Apparatur 2" der USP XXIII (The United States Pharmacopeia USP XXIII 1995, Seite 1791 bis 1792) gemäß der Rührflügelmethode untersucht. Dazu wurde die Wirkstofffreisetzung in einer gängigen Freisetzungsapparatur der Firma ERWEKA bestimmt. Die Tabletten wurden in Puffer pH=6,8 (10%ig) nach Deutschem Arzneibuch 9. Ausgabe mit Tensidzusatz bei 37°C und 100 Upm inkubiert. Innerhalb von 24 Stunden setzten die Tabletten den Wirkstoff gemäß Tabelle frei. Die Freisetzungsmengen in der Tabelle sind als prozentualer Anteil der freigesetzten Wirkstoffmenge, bezogen auf die gesamte ursprüngliche Wirkstoffmenge im Kern angegeben.

Freisetzung	Beispiel 1	Beispiel 2	Beispiel 3	Beispiel 4	Vergleichs-beispiel 1	Vergleichs-beispiel 2
240 min.	12,5%	10%	32,5%	30,8%	5%	13,6%
480 min.	41,7%	30%	67,5%	64,5%	22%	33,6%
720 min.	57,5%	53,3%	76,7%	75,8%	37%	48,2%
960 min.	65%	60,8%	81,7%	80,8%	45%	54,5%
1440 min.	70%	71,7%	87,5%	86,7%	51%	62,7%

Tabelle Freisetzung von Wirkstoff aus Tabletten gemäß Beispiel 1-4 und aus Tabletten der Vergleichsbeispiele 1-2

Die Ergebnisse zeigen, daß das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem den Wirkstoff im relevanten Zeitintervall - je nach angestrebter Freisetzungsrate - nahezu vollständig freisetzt, wohingegen die osmotischen Arzneimittelfreisetzungssyteme aus dem Stand der Technik den Wirkstoff am Ende der Freisetzung nur unvollständig freisetzen. Dabei ist davon auszugehen, daß nach einem Zeitraum von 24 Stunden eine Freisetzung an absorptionsrelevanten Stellen des Gastrointestinaltrakts nicht mehr stattfindet und die osmotischen Arzneimittelfreisetzungssysteme das Plateau ihrer Freisetzung erreicht haben. Die erfindungsgemäßen Beispiele 1 und 2 einerseits und 3 und 4 andererseits verdeutlichen den Einfluß der Feuchtgranulation im Unterschied zur Trockengranulation. Wie oben dargelegt, bewirkt die Feuchtgranulation häufig eine bessere Benetzbarkeit der Bestandteile des Tablettenkerns, wodurch die eintretende Gastrointestinalflüssigkeit den Kern besser durchdringt, was zu einer rascheren und vollständigeren Freisetzung des Wirkstoffs führt. Die Feuchtgranulation ist daher bevorzugt. Der Einsatz der Feuchtgranulation wird durch die Verwendung der speziellen wasserquellbaren Polymere in dem erfindungsgemäßen osmotischen Arzneimittelfreisetzungssystem, welche im Gegensatz zu den im Stand der Technik verwendeten Polyethylenoxiden keiner organischen Lösungsmittel bedürfen, praktisch erst ermöglicht. Der Vergleich zwischen den erfindungsgemäßen Beispielen 1 und 2 bzw. 3 und 4 zeigt, daß eine höhere Hüllackauftragsmenge am Anfang der Freisetzung zu einer gewissen Verzögerung (Lag-Zeit) führt, und die Freisetzungsrate aufgrund der

geringeren Eintrittsgeschwindigkeit der Gastrointestinalflüssigkeit verlangsamt wird. Über einen längeren Zeitraum werden jedoch weitgehend unabhängig von der Lackauftragsmenge etwa gleich hohe Freisetzungsmengen in den erfindungsgemäßen Beispielen erzielt.

Der Vergleich zwischen Beispiel 2 der Erfindung und Vergleichsbeispiel 1 zeigt, daß das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem bei etwa gleicher Lackauftragsmenge und Lackzusammensetzung sowie vergleichbarem Herstellungsverfahren (Trockengranulation bzw. Direkttablettierung) eine deutlich höhere Endfreisetzung bei annähernd gleichen Anfangsfreisetzungsraten aufweist. Dies bedeutet, daß das erfindungsgemäße osmotische Arzneimittelfreisetzungssystem auch zu einem späteren Zeitpunkt noch mit einer relativ hohen Freisetzungsrate den Wirkstoff freisetzt, wenn die Freisetzung des Wirkstoffs des osmotischen Arzneimittelfreisetzungssystems des Vergleichsbeipiels praktisch bereits zum Erliegen gekommen ist. Das bedeutet, daß ein großer Anteil des Wirkstoffs des Vergleichsbeispiels in der Tablette verbleibt und somit ungenutzt ausgeschieden wird. Auch bei Vergleichsbeispiel 2 wird eine niedrige Freisetzungsrate in einem späteren Zeitpunkt der Freisetzung beobachtet.

Patentansprüche

1. Osmotisches Arzneimittelfreisetzungssystem, bestehend aus

- einer Hülle aus einem wasserdurchlässigen, für die Komponenten des Kerns undurchlässigen Material, die mindestens eine Öffnung aufweist, und

- einem Kern, enthaltend

  - 15 bis 35 Gew.-% eines pharmazeutischen Wirkstoffs
  - 20 bis 50 Gew.-% Xanthan
  - 10 bis 30 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

2. Osmotisches Arzneimittelfreisetzungssystem nach Anspruch 1, das einen Kern umfaßt, der enthält:

- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
- 25 bis 40 Gew.-% Xanthan
- 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

wobei gegebenenfalls die Differenz zu 100 Gew.-% durch mindestens einen Bestandteil gebildet wird, der aus der Gruppe ausgewählt wird, die aus weiteren hydrophilen quellbaren Polymeren, osmotisch aktiven Zusätzen und

pharmazeutisch annehmbaren Zusatzstoffen besteht, die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

3. Osmotisches Arzneimittelfreisetzungssystem nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß der Kern mindestens einen osmotisch aktiven Zusatz enthält.

4. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß der Kern mindestens einen osmotisch aktiven Zusatz sowie mindestens einen pharmazeutisch annehmbaren Zusatzstoff enthält.

5. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 4, das einen Kern umfaßt, der enthält:

- 20 bis 30 Gew.-% eines pharmazeutischen Wirkstoffs
- 25 bis 40 Gew.-% Xanthan
- 10 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,
- 10 bis 30 Gew.-% einer osmotisch aktiven Substanz,
- 8 bis 20 Gew.-% mindestens eines pharmazeutisch annehmbaren Zusatzstoffes,

wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

6. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der Wirkstoff ein schwerlöslicher Wirkstoff ist.

7. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß der Wirkstoff ein schwerlöslicher Wirkstoff ist, der auch noch im Dickdarm resobiert wird.

8. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß der Wirkstoff ein Dihydropyridin ist.

9. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß der Wirkstoff Nifedipin ist.

10. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 9, dadurch gekennzeichnet, daß der osmotisch aktive Zusatz Natriumchlorid ist.

11. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß der pharmazeutisch annehmbare Zusatzstoff ausgewählt wird aus pharmazeutisch annehmbaren Pufferstoffen, pharmazeutisch annehmbaren Gleitmitteln, pharmazeutisch annehmbaren Sprengmitteln sowie pharmazeutisch annehmbaren Tablettierhilfsmitteln.

12. Osmotisches Arzneimittelfreisetzungssystem nach Anspruch 11, dadurch gekennzeichnet, daß der pharmazeutisch annehmbare Pufferstoff Natriumbicarbonat, das pharmazeutisch annehmbare Gleitmittel Magnesiumstearat ist, das pharmazeutisch annehmbare Sprengmittel Natriumcarboxymethylstärke, und ein pharmazeutisch annehmbares Tablettierhilfsmittel.

13. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 12, das einen Kern umfaßt, der enthält:

- 19 bis 23 Gew.-% eines pharmazeutischen Wirkstoffs
- 28 bis 32 Gew.-% Xanthan
- 15 bis 20 Gew.-% eines Vinylpyrrolidon-Vinylacetat-Copolymers,

- 15 bis 20 Gew.-% Natriumchlorid
- 5 bis 7 Gew.-% Natriumbicarbonat
- 6 bis 9 Gew.-% Natriumcarboxymethylstärke
- <1 Gew.-% Magnesiumstearat

wobei die Gew.-%-Angaben auf das Gesamtgewicht der Kernbestandteile bezogen sind und die Summe der Kernbestandteile zu 100% aufaddiert.

14. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 13, dadurch gekennzeichnet, daß es in Tablettenform vorliegt.

15. Verfahren zur Herstellung des osmotischen Arzneimittelfreisetzungssystems nach irgendeinem der Ansprüche 1 bis 14, dadurch gekennzeichnet, daß die Bestandteile des Kerns miteinander vermischt werden, gegebenenfalls trocken oder feucht granuliert werden, tablettiert werden und der so entstandene Kern mit der Hülle beschichtet wird.

16. Osmotisches Arzneimittelfreisetzungssystem nach irgendeinem der Ansprüche 1 bis 14 zur Verwendung als Arzneimittel bei Menschen oder Tieren.

17. Verwendung des osmotischen Arzneimittelfreisetzungssystems nach irgendeinem der Ansprüche 1 bis 14 zur Herstellung eines Arzneimittels zur Behandlung von Bluthochdruck, koronaren Herzerkrankungen, cerebralen Leistungsstörungen und zur Therapie neurologischer Defizite nach Subarachnoidalblutung.

18. Verwendung des osmotischen Arzneimittelfreisetzungssystems nach Anspruch 17 zur Herstellung eines Arzneimittels zur Behandlung von Bluthochdruck und koronaren Herzerkrankungen.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/06454

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/44

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 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.
A	EP 0 277 092 A (CIBA GEIGY AG) 3 August 1988 cited in the application see page 1, line 61 - page 2, line 6 see page 3, line 34-38 see page 3, line 64 - page 4, line 18 see page 4, line 38-42 see example 4 see claims 1,4 ---	1-18
A	EP 0 740 934 A (BAYER AG) 6 November 1996 see page 2, column 1, line 3-6 see page 1, column 2, line 27-38 see page 1, column 2, line 45 see page 2, column 3, line 26-32 see page 2, column 4, line 27-36 see example 11 see claims 1,2,4 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1999	10/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	La Gaetana, R

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0281

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/06454

C.(Continuation) 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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A	WO 97 39050 A (MENDELL CO INC EDWARD ;BAICHWAL ANAND R (US)) 23 October 1997 see page 4, line 16-23 see page 5, line 9-14 see page 5, line 23-26 see page 21; tables 1,2 -----	1-18

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INTERNATIONALER RECHERCHENBERICHT

Inte ionales Aktenzeichen
PCT/EP 98/06454

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 6 A61K9/44

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 6 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	EP 0 277 092 A (CIBA GEIGY AG) 3. August 1988 in der Anmeldung erwähnt siehe Seite 1, Zeile 61 - Seite 2, Zeile 6 siehe Seite 3, Zeile 34-38 siehe Seite 3, Zeile 64 - Seite 4, Zeile 18 siehe Seite 4, Zeile 38-42 siehe Beispiel 4 siehe Ansprüche 1,4 --- -/--	1-18

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
2. März 1999	10/03/1999

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	La Gaetana, R

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Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

0284

INTERNATIONALER RECHERCHENBERICHT

Inte onales Aktenzeichen
PCT/EP 98/06454

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

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C07D 413/10, A61K 31/38, 31/42

A1

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60/100,185	14 September 1998 (14.09.98)	US

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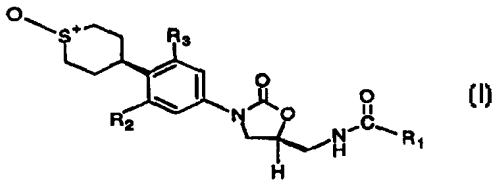
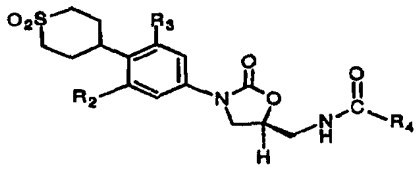


(I)



(II)

(57) Abstract

The present invention provides compounds of formula (I) and formula (II) useful as antimicrobial agents wherein R_1 is methyl, ethyl, cyclopropyl, or dichloromethyl; R_2 and R_3 are independently hydrogen or fluoro; R_4 is ethyl or dichloromethyl. The invention also relates to a novel assay for determining the inhibitory activity of oxazolidinones to human monoamine oxidase.

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S-OXIDE AND S,S-DIOXIDE TETRAHYDROTHIOPYRAN PHENYLOXAZOLIDINONES

FIELD OF THE INVENTION

The present invention relates to sulfur oxidized tetrahydrothiopyran N-phenyloxazolidinone compounds in which the phenyloxazolidinone moiety is linked with a thiopyran ring through a carbon-carbon bond. The invention also relates to a novel assay for determining the inhibitory activity of oxazolidinones to human monoamine oxidase.

BACKGROUND OF THE INVENTION

The oxazolidinone antibacterial agents are a novel synthetic class of antimicrobials with potent activity against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, gram-negative aerobic bacteria such as H. *influenzae* and M. *catarrahlis*, as well as anaerobic organisms such as bacteroides and clostridia species, acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*. It is also known that as a chemical compound class, oxazolidinones inhibit monoamine oxidase (MAO), the enzyme responsible for preventing acute blood pressure elevation by the endogenous and dietary amine, tyramine. Accordingly, there is a demand to discover oxazolidinone antibiotics which possess minimum MAO inhibitory activity to eliminate the related side effects from potential drug-drug interactions. There is also currently an interest in developing a high throughput screening assay to determine the MAO inhibitory activity of oxazolidinone antibiotics.

INFORMATION DISCLOSURE

International Publication No. WO 97/09328; pending U.S. application, Serial No. 08/696,313, discloses phenyloxazolidinones having a C-C bond to 4-8 membered heterocyclic rings, which generically covers the compounds of the present application.

International Publication No. WO 97/30995 discloses antibiotic oxazolidinone derivatives.

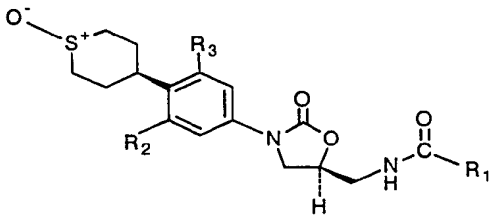
Other references that disclose aromatic heterocycles attached to a phenyloxazolidinone include European Patent Publication No. 0352 781 A2, International Publication No. WO 9309103-A1 and U.S. Patent Nos. 5,130,316,

5,254,577 and 4,948,801.

Additional references of general interest include: Castagnoli Jr. et al., Synthesis and Elective Monoamine Oxidase B-Inhibiting Properties of 1-Methyl-1,2,3,6-Tetrahydropyrid-4-yl Carbamate Derivatives: Potential Prodrugs of (R)- and (S)-Nordeprenyl, *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996); Walter Weyler and J. I. Salach, "Purification and Properties of Mitochondrial Monoamine Oxidase Type A from Human Placenta", *J. of Bio. Chem.*, Vol. 260, No. 24, pp. 13199-13207 (1985) (10/25/85). J. I. Salach and Walter Weyler, Preparation of the Flavin-Containing Aromatic Amine Oxidases of Human Placenta and Beef Liver, *Methods Enzymol.*, Vol. 142, pp 627-623 (1987); Joseph J. P. Zhou, et al., "Direct Continuous Fluorometric Assay for Monoamine Oxidase B", *Analytical Biochemistry*, Vol. 234, pp. 9-12 (1996); Matthew J. Krueger, et al., "An Examination of the Reliability of the Radiochemical Assay for Monoamine Oxidases A and B", *Analytical Biochemistry*, Vol. 214, pp. 116-123 (1993); Keith F. Tipton, et al., "Commentary - The Radiochemical Assay for Monoamine Oxidase Activity - Problems and Pitfalls", *Biochemical Pharmacology,* Vol. 46, No. 8, pp. 1311-1316 (1993).

SUMMARY OF THE INVENTION

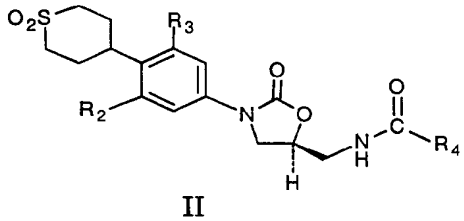
In one aspect, the present invention is a compound of formula I



I

or pharmaceutically acceptable salts thereof wherein R_1 is methyl, ethyl, cyclopropyl, or dichloromethyl; R_2 and R_3 are the same or different and are hydrogen or fluoro. The formula I of the invention embraces both *tran-* and *cis-* isomers.

In another aspect, the present invention is a compound of formula II



II

or pharmaceutically acceptable salts thereof wherein R_2 and R_3 are the same as defined above; R_4 is ethyl or dichloromethyl.

Preferably, in the above formula I, R_1 is methyl or ethyl.

Preferably, in the above formula II, R_4 is ethyl.

Also preferably, compounds of formulas I and II are mono-fluoro compounds.

Preferred compounds of the present invention are:

a. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

b. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,

c. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide,

d. [4(S)-cis]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

e. (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,

f. (S)-(-)-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

g. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,

h. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide, or

i. [4(S)-trans]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

More preferred is compound [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

In still another aspect, the present invention provides a method of assaying an oxazolidinone antibiotic's MAO inhibitory activity, which comprises the steps of

a) incubating an oxazolidinone with a monoamine oxidase in a buffer solution having pH value from about 7.0 to about 7.5;

b) adding 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine into said incubating solution; and

c) determining the monoamine oxidase inhibitory activity of said oxazolidinone.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides sulfur oxidized tetrahydrothiopyran phenyloxazolidinone of formula I and formula II as defined above. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens as disclosed above. In particular, it has been discovered that, while oxazolidinones as a chemical compound class are inhibitors of human monoamine oxidase A (MAO A) and monoamine oxidase B (MAO B), the compounds of the present invention have unexceptedly weak MAO inhibitory activity, which indicates that these compounds possess the capacity to minimize or eliminate potential drug-drug interactions since strong inhibition of monoamine oxidase can result in altered clearance rates for other compounds normally metabolized by it, including several pharmaceuticals.

The present invention also provides a novel spectrophotometric assay for determining the ability of an oxazolidinone to inhibit human monoamine oxidases. MAO A and MAO B are membrane bound flavoproteins localized in the outer mitochondrial membrane. The two enzymes prefer different substrate in catalyzing the oxidative deamination of biogenic and xenobiotic amines. Historically, MAO enzymes have been assayed by radioactive end point (discontinuous) methods using two different substrates. These methods have been criticized because as commonly practiced, they lack the proof of linearity of the reaction time course under prevailing assay conditions. The use of these methods are also inadequate due to their cumbrous nature when screening a large number of compounds in a short period of time. The methods involve multiple processing steps including solvent extraction of reaction products. These steps lead to inaccuracies in the resulting data. See: Matthew J. Krueger, et al., "An Examination of the Reliability of the Radiochemical Assay for Monoamine Oxidases A and B", *Analytical Biochemistry*, Vol. 214, pp. 116-123 (1993); Keith F. Tipton, et al., "Commentary - The Radiochemical Assay for Monoamine Oxidase Activity - Problems and Pitfalls", *Biochemical Pharmacology,* Vol. 46, No. 8, pp. 1311-1316 (1993).

We have now developed a continuous, visible, high throughput screening spectrophotometric assay of MAO based on a colored product of oxidation of a chromogenic substrate, 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine. The assay works equally well with MAO-A and MAO-B. It is sensitive, linear and tolerant of the low turbidity level introduced by the solubilized and partially purified MAO A and MAO B. The reaction product is stable for many hours and the reaction rates for both enzymes are linear functions of time and enzyme concentration. The assay has been successfully adapted to a microtiterplate format, therefore, it can

provide information on thousands of tested oxazolidinone compounds in a short period of time. Even in the microtiterplate screening format, accurate information concerning the linearity of the reaction rate under prevailing assay conditions is obtained.

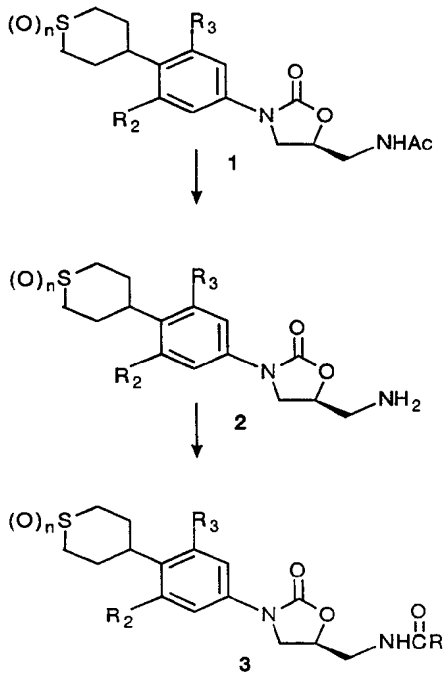
In addition, while evaluation of oxazolidinone compounds' MAO inhibitory activity is the most important utility of this assay, the present invention can be used to detect any inhibitor of MAO enzymes.

For the purpose of the present invention, the term "pharmaceutically acceptable salts" refers to salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citrate, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

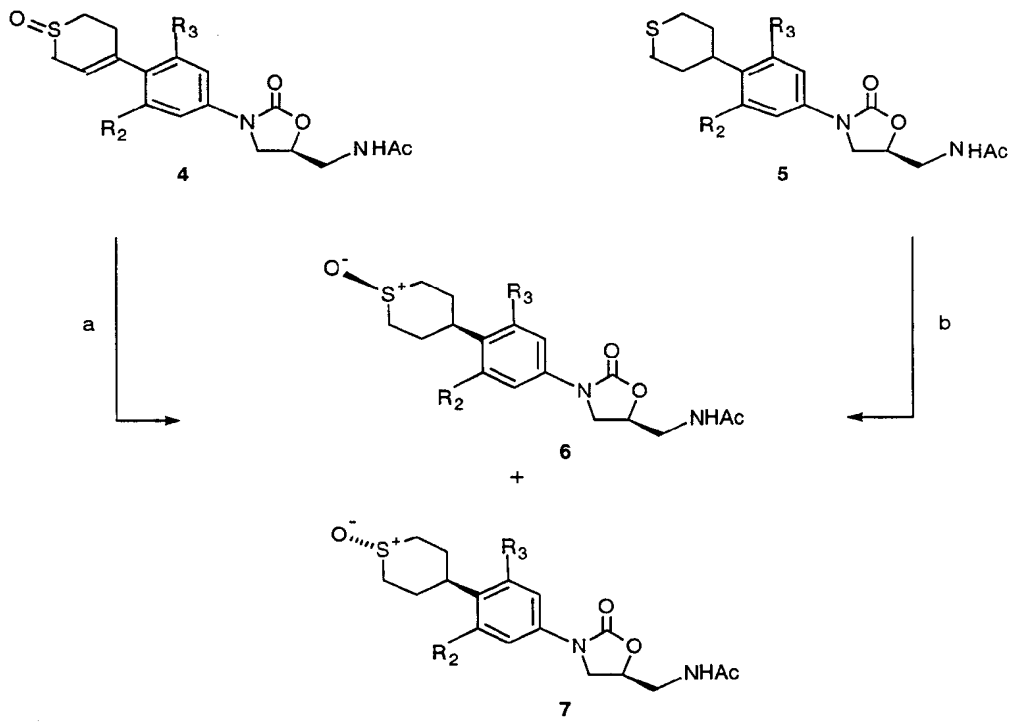
Compounds of the present invention may be prepared in accordance to Schemes I and II following methodology known to those skilled in the art. Briefly, as shown in Scheme I, hydrolysis of the N-acetyl oxazolidinone **1** with hydroxylamine hydrochloride, for instance, provides the amine **2**. Treatment of structure **2** with an acid chloride or anhydride in the presence of a base affords N-acyl oxazolidinone **3**, wherein n is 1 or 2, and R is R_1 or R_4 as defined above. Structure **1** in which n is 2 can be obtained according to the procedures disclosed in International Publication No. WO 97/09328; structure **1** in which n is 1 can be prepared as shown in Scheme II.

Compound **4** in Scheme II, which can be obtained according to the procedures disclosed in International Publication No. WO 97/09328, may be reduced to the corresponding cis- and trans-sulfoxides **6** and **7** by catalytic hydrogenation in the presence of an appropriate catalyst and a suitable solvent, as depicted in route a. Alternatively, sulfide **5**, which may be isolated as a by-product in the reduction shown in route a or synthesized by the reduction of **6** or **7** with a sulfonic acid-sodium iodide system, can be oxidized with an appropriate oxidizing agent such $NaIO_4$ or meta-chloroperoxybenzoic acid in an appropriate solvent to provide **6** and **7**, as depicted in route b of Scheme II. The isomeric mixture of **6** and **7** can be separated by chromatography.

SCHEME I



SCHEME II



These compounds are useful for the treatment of microbial infections, including ophthalmologic infections, in humans and other warm blooded animals, under both parental and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formulas I and II of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipient employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol

systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compounds of formula I or II according to this invention.

The quantity of active component, that is the compound of formula I or II according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, topically, transdermally, and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of formulas I and II according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to formula I or II as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include,

for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compounds according to formula I or II generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of formulas I and II according to this invention are advantageously administered orally in solid and liquid dosage forms.

The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The in vitro activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically", 3rd. ed., published 1993 by the National Committee for Clinical Laboratory Standards, Villanova, Pennsylvania, USA. The activity of compounds of this invention against *Staphylococcus aureus* and H. *influenzae* is shown in Table 1.

The continuous spectrophotometric assay for measuring MAO activity is based on a colored oxidation product of the chromogenic substrate, 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine, by MAO enzymes. The product is stable for many days at room temperature. The conversion of the substrate to the oxidation product is followed continuously from the moment of mixing of the MAO enzyme with the substrate and the initial reaction rate curve is directly observed. The bright yellow-green oxidation product has a peak absorption at 421 nm with a broad band that can be measured between 390 nm to 440 nm. Thus, the assay can be performed on the least sophisticated spectrophotometric equipment. The substrate itself is colorless; and does not spontaneously convert to product under conditions of the assay; thus, there is no interfering background rate.

The assay is sensitive, which allows accurate rate measurements at very low levels of change in the substrate concentration (<1%). The sensitivity of the assay permits measurements to be made on very low concentrations of the MAO enzymes, whether pure or in tissue homogenates. The assay is not susceptible to background interference from biologically derived materials all of which absorb between 210-350 nm.

The assay shows a linear reaction rate over a wide range of MAO enzymes, of the substrate, and of oxazolidinones concentrations and over a considerable portion

of the progress curve at any substrate or enzyme concentration. For example, the assay shows a linear reaction rate at final oxazolidinone's concentration from about 1 mM to about 1 nM; at any concentration of the enzymes which is sufficient to produce an absorbance change of 0.0005-0.05/minute at 421 nm; and at the substrate's concentration from about 10 μM to about 10 mM. The reaction rate is also linear over long time intervals (up to 90 minutes) even at low enzyme concentrations. These properties permit a highly accurate rate determination as a function of substrate concentration, enzyme concentration or oxazolidinone inhibitor concentration.

The assay may be carried out in a buffer solution which does not adversely affect the reaction and provides a pH value at a range from about 7.0 to 7.5. The preferred buffer solution is sodium phosphate. The preferred pH value for assay is about 7.3. Further, the assay is preferably conducted at a temperature from about 25 °C to about 40 °C. The most preferred assay temperature is about 37 °C.

The chromogenic substrate 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine can be prepared as described in N. Castagnoli Jr. et al., *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996) and the references cited within. The substrate is prepared as a 10-15 mM stock solution in 50 mM sodium phosphate. The solution is kept on ice or frozen and are typically diluted 1/10-1/100 by 50 mM sodium phosphate (pH = 7-7.5) at the time of assay.

Human placental MAO A is solubilized and purified as described in N. Castagnoli Jr. et al., *J. Med Chem.* Vol. 39, pp. 4756-4761 (1996) and J. I. Salach et al., *J. of Bio. Chem.*, Vol. 260, p. 13199 (1985). The human placental MAO A is obtained as a concentrated solution (5 nmols per ml). Bovine liver MAO B is purified as described N. Castagnoli Jr. et al., *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996) and J. I. Salach et al., *Methods Enzymol.*, Vol. 142, pp 627-623 (1987). The bovine liver MAO B is obtained as a concentrated solution (8 nmols per ml). Working stocks of the enzyme solutions are made by 1/50 dilution of initial stocks into 50 mM sodium phosphate and optionally 10% glycerol. The solutions are kept on ice until final dilution into the assay. Alternatively, the frozen MAO enzymes may be diluted 800-3200 fold into the 50 mM sodium phosphate buffer immediately before use. This method is useful when screening a large number of oxazolidinones.

Oxazolidinones are prepared in DMSO at a concentration of 50 mM. Serial dilutions of the 50 mM stock solution are made in DMSO to form additional stock solutions ranging from 20 mM to 0.3125 mM. The stock solutions are then frozen until use. The stocks are diluted 1/100 into the final enzyme assay volume at the

time of assay.

Typically, the enzyme, along with an oxazolidinone inhibitor, are preincubated for approximately 15 minutes in the sodium phosphate buffer prior to assay. The reactions are started by addition of the substrate. Initial velocities are generally collected over an interval of one to sixty minutes.

The assay functions well in the spectrophotometer cuvette for evaluating single oxazolidinone's MAO inhibitory activity. The assay has also been successfully adapted to operate in high throughput microtiterplate format (i.e., 96, 384 and 1536 well plate readers). Hundreds of assays can be run simultaneously. Assay volumes are 250 µL and the wells have an effective path length of 0.75 cm. Generally, the final composition of the assay in the microtiterplate comprises 0.05 mM sodium phosphate (pH = 7.3), oxazolidinone having concentration ranging up to 500 µM, 1% DMSO, 80µM substrate (MAO A) or 200µM substrate (MAO B), and sufficient enzyme to produce an absorbance change from 0.0005 to 0.050 per minute at 421 nm. The reaction is run at 37 °C, and rapid temperature equilibration of the assay solution is achieved by preincubating the plate and stock solutions at about 37 °C. The reaction is followed by recording the increase in absorbance at 421 nm. The oxidation product has an extinction coefficient of 25,000 M^{-1} cm^{-1} at 420. See: N. Castagnoli Jr. et al., *J. Med Chem.*, Vol. 39, pp. 4756-4761 (1996). Initial rates are determined by linear regression of the progress curves over an absorbance change of 0.06-0.12 at 421 nm. This range represents a substrate consumption of approximately 5% in the assay. The percentage inhibition of an oxazolidinone is determined from the following equation

$$\% \text{ Inhibition} = 100\{1 - [\text{rate}(I) - \text{rate (negative control)}]/[\text{rate (positive control)} - \text{rate (negative control)}]\}$$

In the above equation, the term "negative control" refers to a complete assay with 1% of DMSO but no MAO enzyme. The term "positive control" refers to a complete assay with 1% of DMSO but no inhibitor. The term "rate (I)" refers to the reaction rate under a complete assay conditions. The term "rate (negative control)" refers to the reaction rate under the negative control condition. The term "rate (positive control)" refers to the reaction rate the under position control condition. In the case where a single oxazolidinone's MAO inhibitory activity is evaluated in the microtiterplate screening format, two replicates of positive control assay and two replicates of negative control assay are run to produce averaged control rates. In

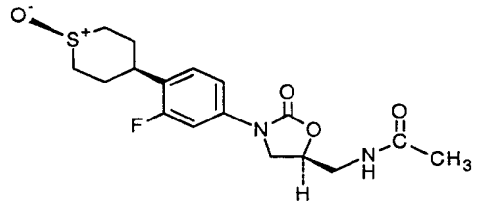
the case where microtiterplate format is used to derive an inhibitory constant (Ki) for an oxazolidinone inhibitor, each plate contains four to eight wells without inhibitor (positive control). These rates are averaged to produce the mean uninhibited control rate for the plate. Each inhibitor is tested at six to eight concentrations. Inhibitory percentage at each concentration is established relative to the uninhibited control rate. Since oxazolidinones are competitive inhibitors of MAO enzymes, the dissociation constant Ki is calculated from the initial velocity data using the following equation:

$$\%\text{Inhibition} = 100[I]/ ([I] + Ki\ (1 + [S]/Km_{(s)})$$

See I. H. Segel, *Enzyme Kinetics.*, Vol. 957, p.105, (1975). Wiley Interscience. NY, NY. In this equation, [S] refers to the concentration of the chromogenic substrate; [I] refers to the concentration of an oxazolidinone inhibitor; and $Km_{[s]}$ refers to the dissociation constant of the substrate for the MAO enzyme. In practice, the data points from the inhibitor experiment are fit to the equation by non-linear least squares regression analysis. The Ki parameter and its standard error are estimated by the regression procedure. A low Ki value indicates that the tested inhibitor possesses a tight binding ability to MAO enzyme, thus, it is a strong MAO inhibitor.

The compounds and their preparations of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

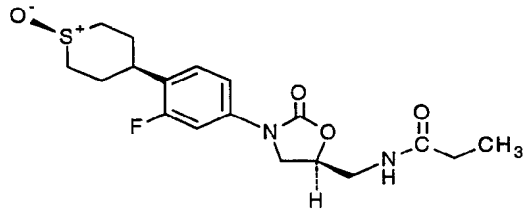
EXAMPLE 1 Preparation of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.



A mixture of (S)-(-)-N-[[3-[3-fluoro-4-(3,6-dihydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S-oxide (4.50 g, can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) and platinum oxide (697 mg) in methanol (164 mL) is shaken on the Parr apparatus under a hydrogen atmosphere at 40 psi for 18 hours. The catalyst is then removed by

filtration through Celite, and the filtrate is concentrated under reduced pressure and the residue chromatographed on silica gel (230 - 400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3/97 - 7/93). Pooling and concentration of those fractions with an R_f = 0.44 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 203 - 204 °C.

EXAMPLE 2 Preparation of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.



Step 1: Preparation of [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone.

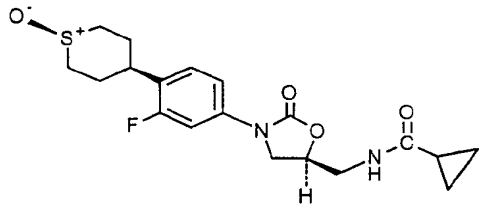
A mixture of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 1, 2.50 g) and hydroxylamine hydrochloride (2.36 g) in pyridine (30.6 mL) and ethanol (3.4 mL) is stirred in a screw-cap vial at 100 °C for 22 hours and at ambient temperature for 16 hours, during which additional hydroxylamine hydrochloride (944 mg) and pyridine (4 mL) is added. The reaction mixture is then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (100 mL) and saline (50 mL), adjusted to pH 11 with solid sodium carbonate and extracted with methanol/methylene chloride (10/90, 5 x 100 mL). The combined organic phase is concentrated under reduced pressure, and the crude product is chromatographed on silica gel (230 - 400 mesh, 150 g), eluting with a gradient of methanol/methylene chloride (6/94 - 10/90). Pooling and concentration of those fractions with an R_f = 0.14 by TLC (methanol/chloroform, 10/90) gives the title compound, mp 159 - 161 °C.

Step 2: Preparation of [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.

A solution of [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 2, Step 1, 150 mg), propionic anhydride (62 µL) and pyridine (75 µL) in methylene chloride is stirred under a nitrogen atmosphere for 66 hours, during which time additional propionic anhydride (12 µL) is added. The reaction mixture is then diluted with water (15 mL) and

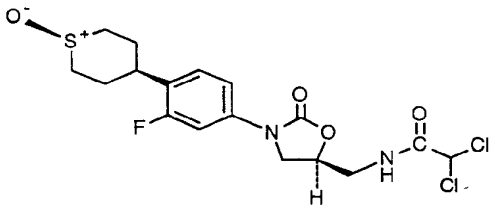
extracted with methylene chloride (2 x 20 mL), and the combined organic phase is washed with saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 35 g), eluting with a gradient of methanol/methylene chloride (3/97 - 5/95). Pooling and concentration of those fractions with an R_f = 0.51 by TLC (methanol/chloroform, 10/90) and recrystallization from methylene chloride/diethyl ether gives the title compound, mp 212 - 214 °C (dec.).

EXAMPLE 3 Preparation of [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl] cyclopropane-carboxamide.



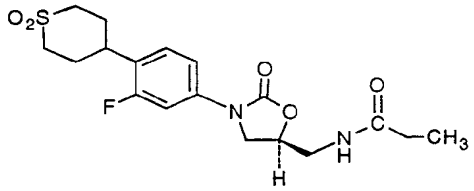
A solution of [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 2, Step 1, 250 mg) and triethylamine (0.16 mL) in methylene chloride (3.1 mL) at 0 °C under a nitrogen atmosphere is treated with cyclopropanecarbonyl chloride (73 µL) and stirred at 0 °C for 2 hours. The reaction mixture is then diluted with methylene chloride (25 mL), washed with water (10 mL) and saline (10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which is chromatographed on silica gel (230 - 400 mesh, 40 g), eluting with methanol/methylene chloride (5/95). Pooling and concentration of these fractions with an R_f = 0.65 by TLC (methanol/chloroform, 10/90) followed by trituration with methylene chloride/diethyl ether (50/50) and filtration gives the title compound, mp 242 - 243 °C (dec.).

EXAMPLE 4 Preparation of [4(S)-cis]-2,2-dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.



Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting dichloroacetyl chloride for cyclopropanecarbonyl chloride, the title compound is obtained, mp 198 - 200 °C (dec.).

EXAMPLE 5 Preparation of (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.



Step 1: Preparation of (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone.

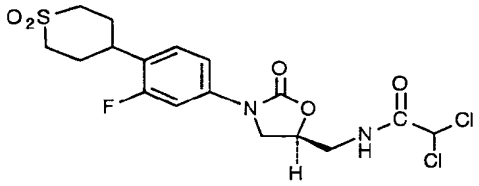
Following the general procedure of EXAMPLE 2, Step 1, and making non-critical variations but substituting (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide (can be obtained according to the procedures disclosed in International Publication No. WO 97/09328) for [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 194 °C (dec.).

Step 2: (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide

Following the general procedure of EXAMPLE 2, Step 2, and making non-critical variations but substituting (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 5, Step 1) for [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone and allowing for a reaction time of 2 hours, the title compound is obtained, mp 200 - 201 °C.

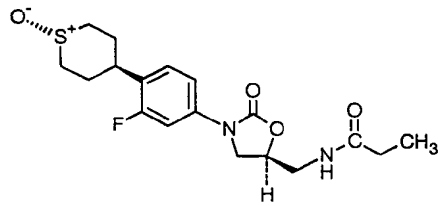
EXAMPLE 6 Preparation of (S)-(-)-2,2-dichloro-N-[[3-[3-fluoro-4-(tetrahydro-

1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.



Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting dichloroacetyl chloride for cyclopropanecarbonyl chloride and (S)-(-)-3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone (EXAMPLE 5, Step 1) for [4(S)-cis]-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone and chromatographing the crude product with methanol/chloroform (2/98), the title compound is obtained, mp 136-137 °C (dec.).

EXAMPLE 7 Preparation of [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.



Step 1: Preparation of (S)-(-)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Following the general procedure of EXAMPLE 1, and making non-critical variations but pooling and concentrating those fractions from the chromatography with an R_f = 0.67 by TLC (methanol/chloroform, 10/90), the title compound is obtained, mp 202 - 205 °C. Anal. Calcd for $C_{17}H_{21}FN_2O_3S$: C, 57.94; H, 6.01; N, 7.95; S, 9.10. Found: C, 57.95; H, 5.98; N, 7.94; S, 8.97.

Step 2: Preparation of [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

A slurry of (S)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (EXAMPLE 7, Step 1, 2.50 g) in methylene chloride (35 mL) at 0 °C under a nitrogen atmosphere is treated with MCPBA (2.16 g, <85%

pure, <10.64 mmol) in two portions. The resulting mixture is allowed to warm to ambient temperature and is stirred for 20 hours, during which time additional MCPBA (360 mg, <85% pure, <1.77 mmol) is added. The reaction is then diluted with methylene chloride (50 mL) and washed with saturated aqueous sodium bicarbonate (50 mL), the aqueous phase is reextracted with methanol/methylene chloride (2 x 50 mL, 5/95), and the combined organic phase is washed with saline (25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude reaction mixture is chromatographed on silica gel (230-400 mesh, 350 g), eluting with a gradient of methanol/methylene chloride (3.5/96.5 - 5/95), and those fractions with an R_f = 0.42 by TLC (methanol/chloroform, 10/90) are pooled and concentrated to give a mixture of the *cis* and *trans* sulfoxide products. Subsequent purification by HPLC (Chiralcel OD column, ethanol eluent) followed by trituration with methylene chloride/diethyl ether (50/50) gives the title compound, mp 211 - 212 °C.

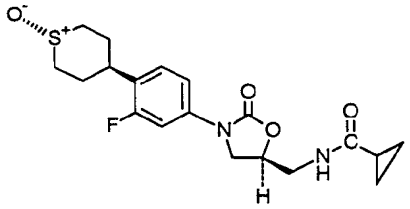
Step 3: Preparation of [4(S)-trans]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone.

Following the general procedure of EXAMPLE 2, Step 1, and making non-critical variations but substituting [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide for [4(S)-cis]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the title compound is obtained, mp 138 - 140 °C.

Step 4: Preparation of [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide.

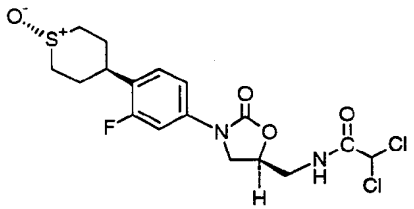
Following the general procedure of EXAMPLE 2, Step 2, and making non-critical variations but substituting [4(S)-trans]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone for [4(S)-cis]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, the title compound is obtained, mp 200 - 202 °C (dec.).

EXAMPLE 8 Preparation of [4(S)-trans]-(-)-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropane-carboxamide.



Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting [4(S)-trans]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone for [4(S)-cis]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, the title compound is obtained, mp 189 - 191 °C.

EXAMPLE 9 Preparation of [4(S)-trans]-2,2-dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.



Following the general procedure of EXAMPLE 3, and making non-critical variations but substituting dichloroacetyl chloride for cyclopropanecarbonyl chloride and [4(S)-trans]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone for [4(S)-cis]-(-)-3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-5-aminomethyl-2-oxazolidinone, the title compound is obtained, mp 206 - 208 °C (dec.).

EXAMPLE 10 Evaluation of Oxazolidinones' Inhibitory Activity to Human MAO-A

The solubilized and purified forms of human MAO-A and the substrate are obtained from Dr. Neal Castagnoli Jr's lab in Department of Chemistry, Virginia Technical University, Blacksburg, Virginia.

Preparation of buffer solutions: sodium phosphate was prepared as a 50 mM stock solution, pH = 7.3 at 37 °C. Preparation of the testing compounds: stock solutions (50 mM) of the test compounds were prepared in DMSO. Serial dilutions of

the 50 mM stocks were made in DMSO to form additional stock solutions ranging from 20 mM to 0.3125 mM. These stocks were then frozen until needed. The stocks were diluted 1/100 into the final enzyme assay volume at the time of assay. A 10 mM stock solution of the chromogenic substrate was prepared in the 50 mM phosphate buffer, aliquoted and then frozen until time of use.

Enzyme Assay- Initial velocity assays were run in a SPECTRAmax 250 microplate spectrophotometer (Molecular Devices Corp., Sunnyvale, CA.). The final composition of the assay solution comprises 0.05 M sodium phosphate (pH = 7.3), 80 µM substrate, inhibitor concentrations ranging up to 500 µM, 1% DMSO, and sufficient enzyme to produce an absorbance change at 421 nm of 0.0005-0.005/ minute. The reactions were run at 37 °C. The reaction was followed by recording the increase in absorbance at 421 nm. Inhibitors were pre-incubated with the MAO A in the reaction mixture for 15 minutes prior to starting the reaction. Ki values were determined from the initial velocity data using the above equation.

The results are also shown in Table 1.

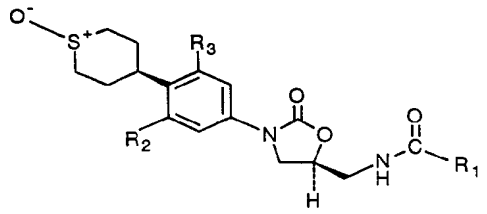
TABLE 1

In vitro activities against S. *aureus* UC® No. 9213 and gram-negative bacteria H. *influenzae* 30063, and inhibitory activity data of human MAO A.

Example No.	MIC (μg/mL) *S. aureus* (UC 9213)	MIC (μg/mL) H. *influenzae* 30063	Ki (μM)
1	4	8	648
2	8	16	>3000
3	8	16	734
4	2	8	2570
5	4	8	3000
6	2	2	>3000
7	4	4	905
8	8	16	>3000
9	1	2	396

CLAIMS

1. A compound of formula I



I

or pharmaceutically acceptable salts thereof wherein:

R_1 is

a) methyl,

b) ethyl,

c) cyclopropyl, or

d) dichloromethyl;

R_2 and R_3 are the same or different and are

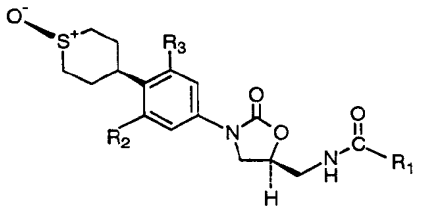
a) hydrogen, or

b) fluoro.

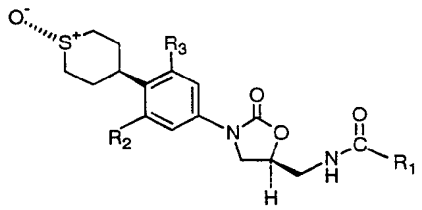
2. A compound of claim 1 wherein R_1 is methyl.

3. A compound of claim 1 wherein R_2 is fluoro; R_3 is hydrogen.

4. A compound of formula I in claim 1 which is



5. A compound of formula I in claim 1 which is



6. A compound of claim 1 which is

a. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide,

b. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,

c. [4(S)-cis]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide,

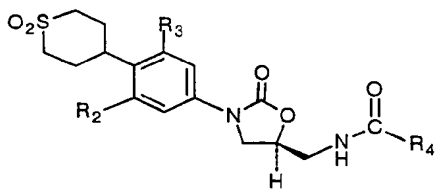
d. [4(S)-cis]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

e. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide,

f. [4(S)-trans]-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]cyclopropanecarboxamide, or

g. [4(S)-trans]-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1-oxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

7. A compound of formula II



II

or pharmaceutically acceptable salts thereof wherein

R_2 and R_3 are the same or different and are

a) hydrogen, or

b) fluoro;

R_4 is

a) ethyl, or

b) dichloromethyl.

8. A compound of claim 7 wherein R_2 is fluoro; R_3 is hydrogen.

9. A compound of claim 7 which is

a. (S)-(-)-N-[[3-[3-Fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]propionamide, or

b. (S)-(-)-2,2-Dichloro-N-[[3-[3-fluoro-4-(tetrahydro-1,1-dioxido-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

10. A use of a compound of Formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament to treat microbial infections in patients comprising:
administering to a patient in need thereof an effective amount of a compound of Formula I as shown in claim 1.

11. A use of a compound of Formula II or pharmaceutically acceptable salts thereof for the preparation of a medicament for treating microbial infections in patients comprising:
administering to a patient in need thereof an effective amount of a compound of Formula II as shown in claim 7.

12. The use of claim 10 wherein said compound of Formula I is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.

13. The use of claim 11 wherein said compound of Formula II is administered orally, parenterally, transdermally, or topically in a pharmaceutical composition.

14. The use of claim 10 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

15. The use of claim 11 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

16. A method of assaying compounds which may have monoamine oxidase inhibitory activity comprising the steps of :

a) incubating a potential inhibitor with a monoamine oxidase in a buffer solution having pH value from about 7.0 to about 7.5;

b) adding 1-methyl-4-(1-methyl-2-pyrryl)-1,2,3,6-tetrahydropyridine into said incubating solution; and

c) determining the monoamine oxidase inhibitory activity of said oxazolidinone.

17. The method of claim 16 wherein said inhibitor is an oxazolidinone antibiotic.

18. The method of claim 16 wherein said buffer solution is a phosphate solution.

19. The method of claim 16 wherein the pH value of said buffer solution is about 7.3.

20. The method of claim 16 wherein the length of incubation is about 15 minutes.

21 The method of claim 16 wherein said monoamine oxidase is monoamine oxidase A.

22. The method of claim 16 wherein said monoamine oxidase is monoamine oxidase B.

23. The method of claim 16 wherein said oxazolidinone is in a final concentration of from about 1 mM to about 1 nM.

24 The method of claim 16 wherein said MAO enzyme is sufficient to produce an absorbance change of 0.0005-0.05/minute at 421 nM.

25. The method of claim 16 wherein said substrate is in a concentration of from about 50 μM to about 500 μM.

26. The method of claim 16 wherein said assaying is performed in a spectrophotometer.

27. The method of claim 16 wherein said assaying is performed in a microtiterplate spectrophotometer.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 98/24526

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/10 A61K31/38 A61K31/42

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

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.
X	WO 97 09328 A (PHARMACIA & UPJOHN CO.) 13 March 1997 cited in the application see page 1, line 30 - page 3, line 31 see page 13, line 16 - line 21 see page 13, line 26 - line 35 see examples 49-51,54,55,63-65 see page 95, formula 52 ---	1,7,10, 11
A	WO 97 30995 A (ZENECA LTD.) 28 August 1997 cited in the application see claims 1,10,11; tables A,B --- -/--	1,7,10, 11

[X] Further documents are listed in the continuation of box C.

[X] 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 March 1999	06/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 98/24526

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 352 781 A (E. I. DU PONT DE NEMOURS AND CO.) 31 January 1990 cited in the application see claims 1,11,12; examples; tables & US 4 948 801 A cited in the application & US 5 130 316 A cited in the application & US 5 254 577 A cited in the application	1,7,10, 11
A	WO 93 09103 A (THE UPJOHN CO.) 13 May 1993 cited in the application see abstract; claim 1	1,7,10, 11
A	US 5 523 403 A (M. R. BARBACHYN) 4 June 1996 see column 40, line 13 - column 41, line 50; claim 1; table 1	1,7,10, 11

1

INTERNATIONAL SEARCH REPORT

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(11) EP 0 930 076 A1

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(54) MEDICINAL COMPOSITIONS

(57) A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents exhibits excellent arteriosclerotic progress inhibitory effects, and is useful as a drug, particularly as a drug for the prevention or treatment of arteriosclerosis.

EP 0 930 076 A1

Description

[Technical Field of the Invention]

[0001] The present invention relates to a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis), and a method which comprises administering in combination effective amounts of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for preventing or treating diseases (particularly arteriosclerosis).

[Background of the Invention]

[0002] The occurrence of atherosclerosis is increasing with the adoption of Western-style diet and the growth of the aged population. This disease is the main cause of such disorders as myocardial infarction, cerebral infarction and cerebral apoplexy, and there is a need for its effective prevention and treatment. Examples of risk factors which cause atherosclerosis include hyperlipemia (particularly hypercholesterolemia), hypertension and saccharometabolism disorders based on insulin resistance. In addition, there are many cases in which these risk factors occur in the form of complications (Syndrome X), and are considered to be mutually interrelated [Diabetes, 37, 1595-1607 (1988)].

[0003] Efforts have been made for the purpose of preventing and treating atherosclerosis by suppression of various risk factors such as hyperlipemia, hypertension and insulin resistance. Although HMG-CoA reductase inhibitors like pravastatin improve hyperlipemia, their inhibitory activity on arteriosclerosis in a case of administration alone is not enough [Biochim. Biophys. Acta, 960, 294-302 (1988)]. In addition, even insulin resistance improving agents like troglitazone do not exhibit sufficient atherosclerosis inhibitory activity in a case of administration alone (Japanese Patent Application (Kokai) No. Hei 7-41423).

[0004] On the other hand, among drugs for the treatment of hypertension, it has been reported that atherosclerotic lesions are suppressed when angiotensin converting enzyme (ACE) inhibitors that inhibit the renin-angiotensin system [Hypertension, 15, 327-331 (1990)] or angiotensin II receptor antagonists [Jpn. Circ. J., 60 (Suppl. I), 332 (1996)] are administered to animals having normal blood pressure and hypercholesterolemia. Angiotensin II not only exhibits vasoconstrictive activity, but also activity that stimulates the production of growth factors such as PDGF [Hypertension, 13, 706-711 (1989)] and activity that stimulates migration of neutrophils and macrophages [Eur. Heart J., 11, 100-107 (1990)]. Although the mechanism in which renin-angiotensin system inhibitors suppress atherosclerosis is not clear at the present time, there is a possibility that the mechanism for suppressing atherosclerosis may be a function at the site of the lesion which is different from their blood pressure lowering action. However, since inhibitors of renin-angiotensin system are unable to lower serum lipids [J. Cardiovasc. Pharmacol., 15, S65-S72 (1990)], their administration alone has limitations on the treatment of arteriosclerosis.

[0005] In addition, although troglitazone, glibenclamide and captopril are administered concomitantly to diabetes patients, there is no suggestion indicated whatsoever relating to the prevention and treatment of arteriosclerosis [J. Clinical Therapeutic & Medicines, 9 (Supp. 3), 39-60 (1993)].

[Disclosure of the Invention]

[0006] As a result of earnestly conducting various research in consideration of the importance of the prevention and treatment of arteriosclerosis, the inventors of the present invention found a method to solve the above-mentioned problems involved in the prior art and to obtain a preventive and/or therapeutic effect on arteriosclerosis by using the combination of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of one or more of insulin resistance improving agents.

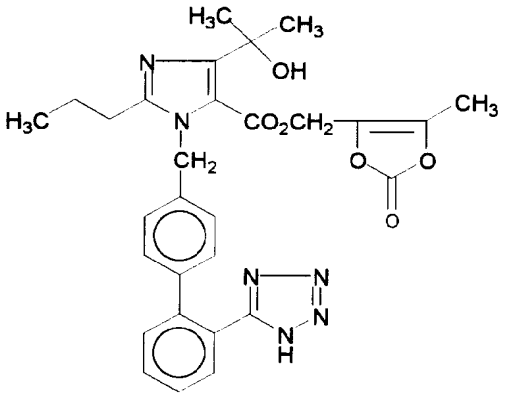
[0007] The present invention provides a pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis), the use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents for preparing a pharmaceutical composition (particularly a composition for prevention or treatment of arteriosclerosis), a method which comprises administering in combination effective amounts of one or more drugs selected

from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to warm-blooded animals for prevention or treatment of diseases (particularly arteriosclerosis), or a pharmaceutical composition for administering at the same time or at the different time one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents (particularly a pharmaceutical composition for prevention or treatment of arteriosclerosis).

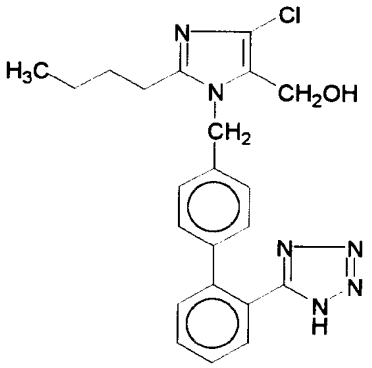
[0008] The active ingredients of the pharmaceutical composition of the present invention (particularly a pharmaceutical composition for the prevention or treatment of arteriosclerosis), or the active ingredients of a method for preventing or treating diseases (particularly arteriosclerosis) include one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.

[0009] Representative examples of angiotensin II receptor antagonists as an active ingredient of the present invention include biphenyltetrazole compounds and biphenylcarboxylic acid compounds described in Japanese Patent Application (Kokai) No. Hei 5-78328, Japanese Patent Application (Kokai) No. Sho 63-23868, Japanese Patent Application (Kokai) No. Hei 4-364171, Japanese Patent Application (Kokai) No. Hei 4-159718 or Japanese PCT Application (Kokai) No. Hei 4-506222, preferably biphenyltetrazole compounds, more preferably CS-866, losartan, candesartan, valsartan or irbesartan, still more preferably CS-866, losartan or candesartan, and most preferably CS-866.

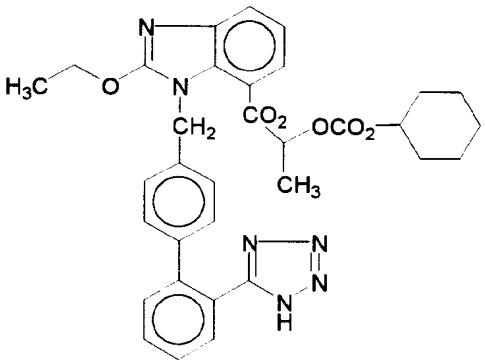
[0010] The following indicates the chemical planar structural formulae of some typical examples of angiotensin II receptor antagonists.



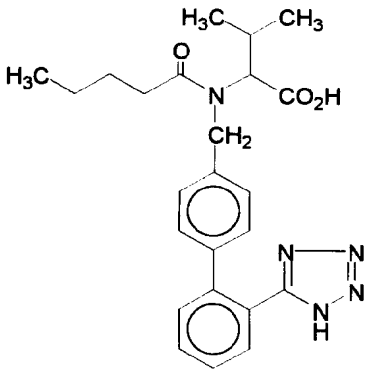
CS-866



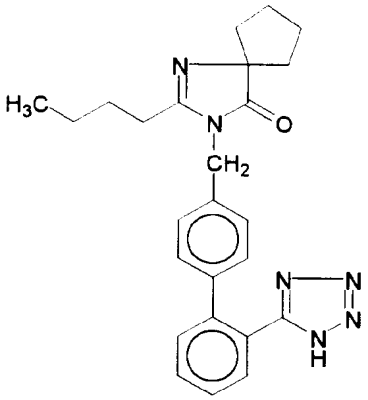
Losartan



Candesartan



Valsartan



Irbesartan

[0011] CS-866 is described in Japanese Patent Application No. (Kokai) No. Hei 5-78328 and the like, and its chemical name is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]imidazole-5-carboxylate. The CS-866 of the present application includes its carboxylic acid derivative, phar-

macologically acceptable esters of its carboxylic acid derivative (such as CS-866) and their pharmacologically acceptable salts.

[0012] Losartan (DUP-753) is described in Japanese Patent Application (Kokai) No. Sho 63-23868, U.S. Patent No. 5,138,069 and the like, and its chemical name is 2-butyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-imidazole-5-methanol. The losartan of the present application includes its pharmacologically acceptable salts (such as losartan potassium salt).

[0013] Candesartan (TCV-116) is described in Japanese Patent Application (Kokai) No. Hei 4-364171, EP-459136, U.S. Patent No. 5,354,766 and the like, and its chemical name is 1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1H-benzimidazole-7-carboxylate. The candesartan of the present application includes its carboxylic acid derivative, pharmacologically acceptable esters of its carboxylic acid derivative (such as TCV-116) and their pharmacologically acceptable salts.

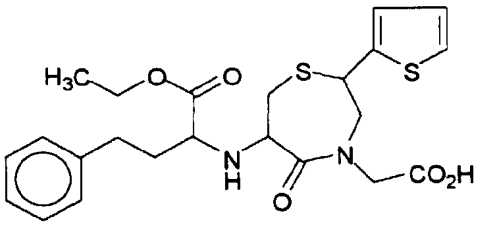
[0014] Valsartan (CGP-48933) is described in Japanese Patent Application (Kokai) No. Hei 4-159718, EP-433983 and the like, and its chemical name is (S)-N-valeryl-N-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)valine. The valsartan of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0015] Irbesartan (SR-47436) is described in Japanese PCT Application (Kokai) No. Hei 4-506222, WO91-14679 and the like, and its chemical name is 2-N-butyl-4-spirocyclopentane-1-[2'-(tetrazol-5-yl)biphenyl-4-ylmethyl]-2-imidazolin-5-one. The irbesartan of the present application includes its pharmacologically acceptable salts.

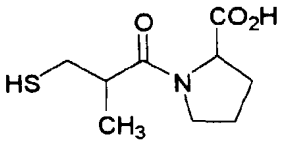
[0016] In addition, where the above-mentioned compounds have asymmetric carbons, the angiotensin II receptor antagonists of the present invention also include optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included.

[0017] Representative examples of the angiotensin converting enzyme inhibitors as an active ingredient of the present invention include tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds described in Japanese Patent Application (Kokai) No. Sho 61-267579, Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,374,829, Japanese Patent Application (Kokai) No. Sho 58-126851, Japanese Patent Application (Kokai) No. Sho 58-206591, Japanese Patent Application (Kokai) No. Sho 57-77651, Japanese Patent Application (Kokai) No. Sho 55-9058, Japanese Patent Application (Kokai) No. Sho 58-203971 and Japanese Patent Application (Kokai) No. Sho 63-258459, preferably temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril or quinapril, more preferably temocapril, captopril or enalapril, and most preferably temocapril.

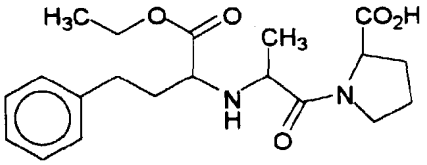
[0018] The following indicates the chemical planar structural formulae of some typical examples of angiotensin converting enzyme inhibitors.



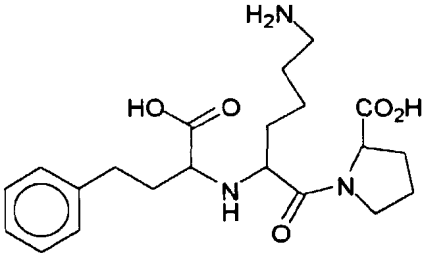
Temocapril



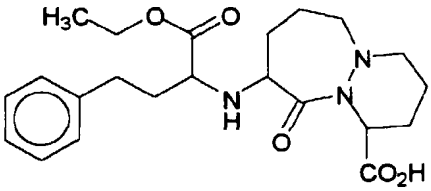
Captopril



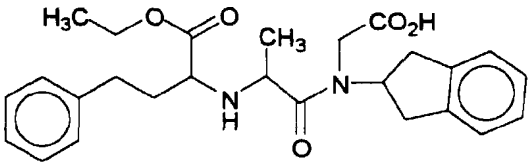
Enalapril



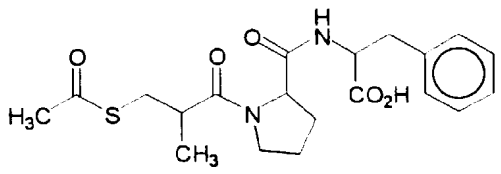
Lisinopril



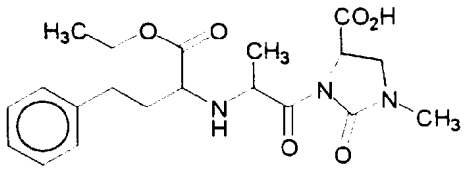
Cilazapril



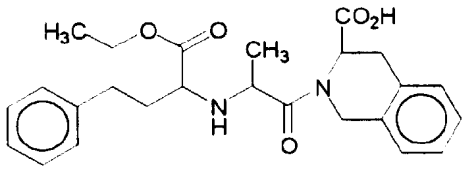
Delapril



Alacepril



Imidapril



Quinapril

[0019] Temocapril is described in Japanese Patent Application (Kokai) No. Sho 61-267579, U.S. Patent No. 4,699,905 and the like, and its chemical name is (+)-(2S,6R)-[6-(1S)-1-ethoxycarbonyl-3-phenylpropylamino]-5-oxo-2-(2-thienyl)perhydro-1,4-thiazepin-4-yl acetic acid. The temocapril of the present application includes its dicarboxylic acid derivatives, its pharmacologically acceptable salts, its pharmacologically acceptable monoesters and its pharmacologically acceptable salts (such as temocapril hydrochloride).

[0020] Captopril is described in Japanese Patent Application (Kokai) No. Sho 52-116457, U.S. Patent No. 4,046,889 and the like, and its chemical name is 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline. The captopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0021] Enalapril is described in U.S. Patent No. 4,374,829 and the like, and its chemical name is N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanyl-L-proline. The enalapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts (such as enalapril maleate).

[0022] Lisinopril is described in Japanese Patent Application (Kokai) No. Sho 58-126851, U.S. Patent No. 4,555,502 and the like, and its chemical name is (S)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline. The lisinopril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0023] Cilazapril is described in Japanese Patent Application (Kokai) No. Sho 58-206591, U.S. Patent No. 4,512,924 and the like, and its chemical name is (1S,9S)-9-[(S)-1-ethoxycarbonyl-3-phenylpropylamino]octahydro-10-oxo-6H-pyridazino[1,2-α][1,2]diazepine-1-carboxylic acid. The cilazapril of the present application includes its pharmacologically acceptable esters and pharmacologically acceptable salts.

[0024] Delapril is described in Japanese Patent Application (Kokai) No. Sho 57-77651, U.S. Patent No. 4,385,051 and the like, and its chemical name is (S)-N-(2,3-dihydro-1H-inden-2-yl)-N-[N-(1-ethoxycarbonyl-3-phenylpropyl)-L-alanyl]glycine. The delapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0025] Alacepril is described in Japanese Patent Application (Kokai) No. Sho 55-9058, U.S. Patent No. 4,248,883 and the like, and its chemical name is 1-(D-3-acetylthio-2-methylpropanoyl)-L-prolyl-L-phenylalanine. The alacepril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

[0026] Imidapril is described in Japanese Patent Application (Kokai) No. Sho 58-203971, U.S. Patent No. 4,508,727 and the like, and its chemical name is (4S)-3-[(2S)-2-[(1S)-1-ethoxycarbonyl-3-phenylpropylamino]propionyl]-1-methyl-2-oxoimidazolidine-4-carboxylic acid. The imidapril of the present application includes its pharmacologically acceptable esters and its pharmacologically acceptable salts.

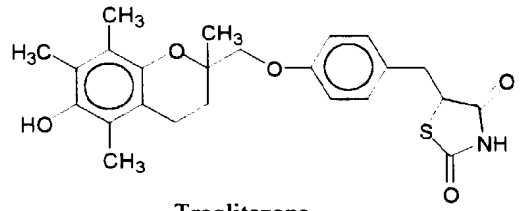
[0027] Quinapril is described in Japanese Patent Application (Kokai) No. Sho 63-258459, U.S. Patent No. 4,761,479 and the like, and its chemical name is (S)-2-[(2S)-2-(1S)-1-ethoxycarbonyl-3-phenylpropylamino)propionyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid. The quinapril of the present application includes its pharmacologically accepta-

ble esters and its pharmacologically acceptable salts.

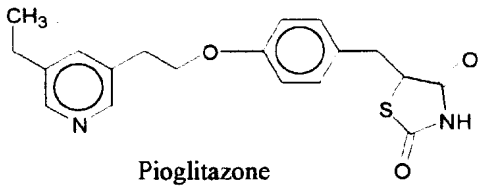
[0028] Where the above-mentioned angiotensin converting enzyme inhibitors of the present invention have asymmetric carbons, said angiotensin converting enzyme inhibitors of the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0029] The insulin resistance improving agents as another active ingredient of the present invention are inherently used for the prevention and treatment of diabetes. Representative examples include thiazolidinedione compounds, oxazolidinedione compounds or oxadiazolidinedione compounds described in Japanese Patent Application (Kokai) No. Hei 4-69383, WO 89/08651, WO 91/07107, WO 92/02520, WO 94/01433, USP-4287200, USP-4340605, USP-4438141, USP-4444779, USP-4461902, USP-4572912, USP-4687777, USP-4703052, USP-4725610, USP-4873255, USP-4897393, USP-4897405, USP-4918091, USP-4948900, USP-5002953, USP-5061717, USP-5120754, USP-5132317, USP-5194443, USP-5223522, USP-5232925 and USP-5260445, preferably thiazolidinedione compounds, more preferably troglitazone, pioglitazone, englitazone or BRL-49653, still more preferably troglitazone or pioglitazone, and most preferably troglitazone.

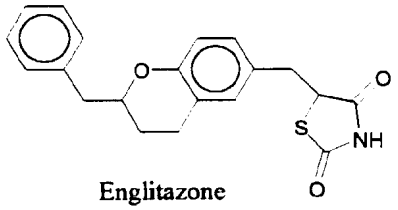
[0030] The following indicates the chemical planar structural formulae of some typical examples of insulin resistance improving agents.



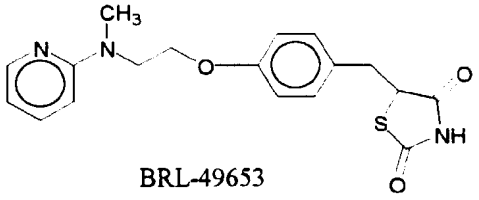
Troglitazone



Pioglitazone



Englitazone



BRL-49653

[0031] Troglitazone is described in Japanese Patent Application (Kokai) No. Sho 60-51189, U.S. Patent No. 4,572,912 and the like, and its chemical name is 5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione. The troglitazone of the present application includes its pharmacologically acceptable salts.

[0032] Pioglitazone is described in Japanese Patent Application (Kokai) No. Sho 55-22636, U.S. Patent No. 4,287,200 and the like, and its chemical name is 5-[4-[2-(5-ethyl-pyridin-2-yl)ethoxy]phenylmethyl]-2,4-thiazolidinedione. The pioglitazone of the present application includes its pharmacologically acceptable salts.

[0033] Englitazone is described in Japanese Patent Application (Kokai) No. Sho 61-271287, U.S. Patent No. 4,703,052 and the like, and its chemical name is 5-(3,4-dihydro-2-benzyl-2H-benzopyran-6-ylmethyl)-2,4-thiazolidinedione. The englitazone of the present application includes its pharmacologically acceptable salts.

[0034] BRL-49653 is described in Japanese Patent Application (Kokai) No. Hei 1-131169, U.S. Patent No. 5,002,953 and the like, and its chemical name is 5-[4-[2-[N-methyl-N-(pyridin-2-yl)amino]ethoxy]phenylmethyl]-2,4-thiazolidinedione. The BRL-49653 of the present application includes its pharmacologically acceptable salts.

[0035] Where the above-mentioned insulin resistance improving agents of the present invention have asymmetric carbons, said resistance improving agents the present invention also include their optical isomers and mixtures of said isomers. Moreover, hydrates of the above-mentioned compounds are also included in the present invention.

[0036] In the present invention, one or more drugs are selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors (preferably the group consisting of angiotensin II receptor antagonists), and one or more insulin resistance improving agents are selected; and preferably the one drug is selected from angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and the other drug is selected

from insulin resistance improving agents to use in combination.

[0037] Preferable examples of the pharmaceutical composition of the present invention are as follows:

(1) a pharmaceutical composition wherein as active ingredients, the angiotensin II receptor antagonists are chosen from biphenyltetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are chosen from tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds;
(2) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril;
(3) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril;
(4) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril;
(5) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan;
(6) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866;
(7) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists;
(8) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan;
(9) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from angiotensin converting enzyme inhibitors;
(10) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is temocapril;
(11) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds;
(12) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;
(13) a pharmaceutical composition wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone; and,
(14) a pharmaceutical composition wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

In addition, a pharmaceutical composition obtained by selecting as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors from the group (1) to (10), by selecting as active ingredients, insulin resistance improving agents from the group (11) to (14) and by combining these groups in an arbitrary manner is also preferable, examples of which are as follows:
(15) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;
(16) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653;
(17) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;
(18) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglita-

zone;

(19) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agents are chosen from troglitazone and pioglitazone;

(20) a pharmaceutical composition wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and as the other active ingredient, the insulin resistance improving agent is troglitazone;

(21) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and as the other active ingredient, the insulin resistance improving agent is troglitazone; and,

(22) a pharmaceutical composition wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and as the other active ingredient, the insulin resistance improving agent is troglitazone.

[Effect of the Invention]

[0038] A drug comprising one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents, which are the active ingredients of the pharmaceutical composition of the present invention (particularly a composition for prevention or treatment of arteriosclerosis), has excellent inhibitory action on aortosclerosis and excellent inhibitory action against onset of xanthochromia occurring in limb joints, and low toxicity. Consequently, it is useful as a drug for the prevention and treatment (particularly for treatment) of arteriosclerosis or xanthochromia.

[0039] According to the present invention, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and insulin resistance improving agents exhibit excellent effects by using two of these agents in combination as compared with being used alone. In addition, these effects can be achieved without requiring that both types of agents be present in the body simultaneously.

[0040] Namely, such effects can be obtained even if both types of agents do not simultaneously have certain concentrations in the blood. According to hypothesis, if two types of agents used in the present invention are both incorporated in vivo and reach the receptors, they have the effect of turning on a switch in vivo. Thus, even if it appears that such effects are not demonstrated at their blood concentrations in course of time after their administration, the switch is actually still on, thereby allowing demonstration of preventive or therapeutic effects on arterial sclerosis possessed by the one type of substance. When the other type of agent is administered in this state, in addition to the preventive or therapeutic effects on arterial sclerosis possessed by that agent, the effects of the drug initially administered are combined to obtain excellent effects. Naturally, since it is convenient clinically to administer two types of agents simultaneously, drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and an insulin resistance improving agent can be administered in the form of a combination drug. In cases where it is undesirable to physically mix both agents simultaneously in consideration of pharmaceutical formulation technology, each individual agent may be administered simultaneously. In addition, as was stated above, since excellent effects are demonstrated even if the two types of agents are not administered simultaneously, each individual agent can also be administered at a suitable interval in succession. The maximum administration interval of the two types of agents to demonstrate the excellent effects brought about by said two types of agents can be determined by clinical or animal studies.

[Industrial Applicability]

[0041] The administration route of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention is typically the oral administration route. Thus, the two types of agents can either be prepared in the form of two separate administrations or in the form of a single administration by physically mixing the two types of agents. The administration form can be, for example, a powder, granules, tablet or capsule and the like, and can be prepared by using conventional pharmaceutical formulation techniques.

[0042] The dose and administration ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and of the insulin resistance improving agents used in the present invention can be changed over a wide range according to various conditions such as the individual activity of each agent, the patient's symptoms, age and body weight, and the like. For example, in the case of insulin resistance improving agents, since the in vivo activities of troglitazone and BRL-49653 by using a diabetic animal model are different, the dose of these two agents may be different by a factor of ten or more. In addition, for both agents consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and insulin resistance improving agents, their doses in the case used for prevention or treatment of arteriosclerosis in the present invention can be lower than their dose for use

as hypotensive agents and diabetes therapeutic agents respectively, which are their well-known applications. In addition, their doses can be made even lower due to the excellent effects resulting from combined use of both types of agents. For example, in the case of using CS-866 and troglitazone for the object of the present invention, their doses are lower than the approximately 5 to 100 mg and approximately 10 to 2000 mg, respectively, which are the doses for adults (mg/day) for use as a hypotensive agent and diabetes therapeutic agent in their well-known applications, being able to be approximately 1 to 80 mg and approximately 1 to 1000 mg, respectively.

[0043] As has been described above, the doses of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of the insulin resistance improving agents can be varied over a wide range, in general, and their doses for adults (mg/day) are approximately 0.5 to 100 mg and approximately 0.05 to 1,500 mg, respectively.

[0044] The ratio of the doses of these two types of agents can also be varied over a wide range, in general, and the dose ratio of the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors to the insulin resistance improving agents can be, in terms of weight ratio, within the range from 1:200 to 200:1.

[0045] In the present invention, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and the insulin resistance improving agents are administered at the respective doses described above once a day or divided among several times per day, and may be administered simultaneously or separately at respectively different times.

[Best Mode for Carrying Out the Invention]

[0046] The present invention will be described more specifically by way of Examples and Preparation examples, but the scope of the present invention is not limited to them.

(Example 1)

Arterial sclerosis Progress Inhibitory Effect

[0047] A certain amount of an agent was administered orally for 32 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: supra (Biochimica et Biophysica Acta), etc.] in groups of 4 to 7 animals each. Incidentally, food consumption was restricted to 120 g/day per animal. Blood samples were collected immediately before administration of the agent and 4, 8, 12, 16, 20, 24, 28 and 32 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. The test animals were subjected to autopsy in the 32nd week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints (%). Those results are shown in Tables 1 and 2.

[Table 1]

Surface Area of Aortic Lesions											
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)							
				Arcuate region		Thoracic part		Abdominal region		Overall	
1	CS-866 + Troglitazone	1 + 25	5	52	10	9	3	13	2	21	4
	CS-866	1	6	68	10	26	8	19	5	34	7
	Troglitazone	25	7	80	7	57	12	32	8	54	9
	Control	-	7	83	6	59	7	39	4	56	4

[Table 2]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
1	CS-866 + Troglitazone	1 + 25	4	75	63	69
	CS-866	1	6	100	100	100
	Troglitazone	25	7	93	86	89
	Control	-	7	100	100	100

(Example 2)

Arterial sclerosis Progress Inhibitory Effect

[0048] A certain amount of an agent was administered orally for 31 weeks to 2-3 months old WHHL rabbits [Watanabe genetically hyperlipemic rabbits: described supra (Biochimica et Biophysica Acta), etc.] in groups of 5 to 7 animals each. Incidentally, food consumption was restricted to 100 g/day per animal. Blood samples were collected immediately before administration of the agent and 8, 16, 24 and 31 weeks after the start of administration to measure total cholesterol levels (mg/dl). There were no changes observed in any of the dose groups as compared with the control group to which no agents were administered. In addition, the test animals were subjected to autopsy in the 31st week to investigate the surface area of aortic lesions (%) and the incidence of xanthochromia in finger joints. Those results are shown in Tables 3 and 4.

[Table 3]

Surface Area of Aortic Lesions							
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Lesion surface area (%)			
				Arcuate region	Thoracic part	Abdominal region	Overall
2	CS-866 + pioglitazone	0.5 + 20	6	62±8	29±10	24±6	36±7
3	CS-866 + BRL-49653	0.5 + 2.5	5	52±5	32±7	25±5	34±5
	CS-866	0.5	7	66±5	41±10	32±8	44±7
	Pioglitazone	20	7	65±6	62±12	32±6	52±8
	BRL-49653	2.5	6	83±2	54±12	29±4	52±5
	Control	-	7	84±5	59±9	32±11	54±8

[Table 4]

Incidence of Xanthochromia in Finger Joints						
Test No.	Test Compound	Dose (mg/kg)	No. of animals	Xanthochromia incidence (%)		
				Fore-limbs	Hind-limbs	Overall
4	Candesartan + troglitazone	1 + 25	7	86	86	86
	Candesartan	1	7	100	100	100
	Troglitazone	25	7	100	86	93
	Control	-	7	100	100	100

(Formulation Example 1)

[0049]

Tablets	
CS-866	4.0 mg
Troglitazone	100.0
Lactose	244.0
Cornstarch	50.0
Magnesium stearate	2.0
	400 mg

[0050] The above-mentioned prescriptions are mixed and formed into tablets with a tablet-making machine to obtain tablets containing 400 mg per tablet.

[0051] These tablets can be provided with a sugar-coating if necessary.

Claims

1. A pharmaceutical composition comprising as its active ingredients one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents.

2. A pharmaceutical composition according to Claim 1 wherein the angiotensin II receptor antagonists are biphenyl tetrazole compounds and biphenylcarboxylic acid compounds and the angiotensin converting enzyme inhibitors are tetrahydrothiazepine compounds, proline compounds, pyridazinodiazepine compounds, glycine compounds, imidazolidine compounds and isoquinoline compounds.

3. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril.

4. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril.

5. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril.

6. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from chosen from CS-866, losartan and candesartan.

7. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is CS-866.

8. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and antagonists and angiotensin converting enzyme inhibitors are angiotensin II receptor antagonists.

9. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan and irbesartan.

10. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are angiotensin converting enzyme inhibitors.

11. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril.

12. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from thiazolidinedione compounds, oxazolidinedione compounds and oxadiazolidinedione compounds.

13. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

14. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

15. A pharmaceutical composition according to Claim 1, wherein as an active ingredient, the insulin resistance improving agent is troglitazone.

16. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

17. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

18. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

19. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

20. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

21. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent is troglitazone.

22. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitor is CS-866, and the insulin resistance improving agent is troglitazone.

23. A pharmaceutical composition according to Claim 1, wherein as active ingredients, the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril, and the insulin resistance improving agent is troglitazone.

24. A pharmaceutical composition according to Claims 1 to 23, wherein said pharmaceutical composition is a composition for preventing or treating arteriosclerosis.

25. The use of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors and of one or more insulin resistance improving agents for preparing a pharmaceutical composition.

26. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

27. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

28. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

29. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

30. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866 and the insulin resistance improving agents are chosen from troglitazone and pioglitazone.

31. The use according to Claim 25, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent is troglitazone.

32. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is CS-866 and the insulin resistance improving agent is troglitazone.

33. The use according to Claim 25, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors is temocapril and the insulin resistance improving agent is troglitazone.

34. The use according to Claims 25 to 33, wherein the pharmaceutical composition is a composition for preventing or treating arteriosclerosis.

35. A method for preventing or treating arteriosclerosis which comprises administering in combiniation an effective amount of one or more drugs selected from the group consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, and one or more insulin resistance improving agents to a warm blooded animal.

36. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril, enalapril, lisinopril, cilazapril, delapril, alacepril, imidapril and quinapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

37. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan, valsartan, irbesartan, temocapril, captopril and enalapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone, pioglitazone, englitazone and BRL-49653.

38. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan, candesartan and temocapril, and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.

39. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.

40. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is CS-866 and the insulin resistance improving agents administered in combination are chosen from troglitazone and pioglitazone.

41. A method according to Claim 35, wherein the drugs consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination are chosen from CS-866, losartan and candesartan, and the insulin resistance improving agent administered in combination is troglitazone.

42. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is CS-866 and the insulin resistance improving agent administered in combination is troglitazone.

43. A method according to Claim 35, wherein the drug consisting of angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors administered in combination is temocapril and the insulin resistance improving agent administered in combination is troglitazone.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02407

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K45/06, A61K31/33

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)
Int. Cl^6 A61K45/06, A61K31/33

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 practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Toru Murakami, Nobuhiro Yamada "Can ACE inhibitors prevent arteriosclerosis? (in Japanese)", Strides of Medicine, (1995), Vol. 174, No. 10. p. 810-813	1 - 34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family 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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
October 1, 1997 (01. 10. 97)	October 21, 1997 (21. 10. 97)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 35 - 43
because they relate to subject matter not required to be searched by this Authority, namely:
Inventions of Claims 35 to 43 pertain to methods for treatment of the human or animal body by therapy.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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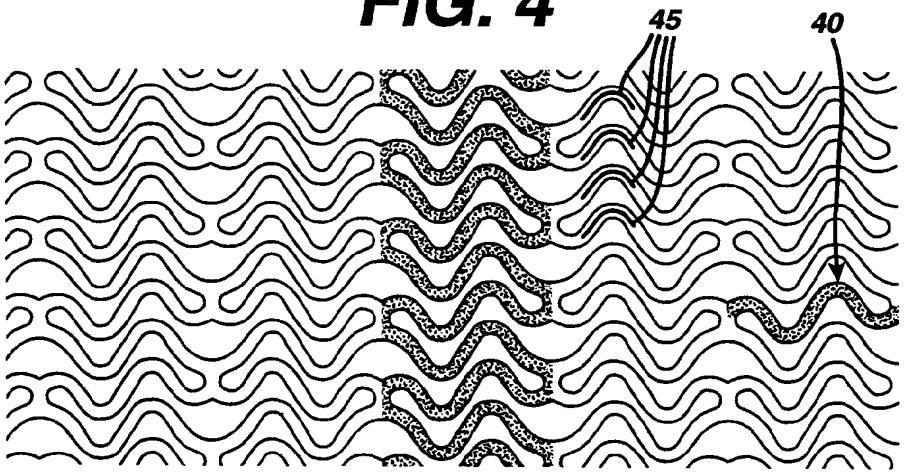
(54) Stent with local rapamycin delivery

(57) Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

FIG. 4



EP 0 950 386 A2

Description

Field of the Invention:

[0001] Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

Background of the Invention:

[0002] Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10-50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3-6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

[0003] Several recent experimental approaches to preventing SMC proliferation have shown promise although the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

[0004] Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and *c-myc* and *c-myb* antinsense oligonucleotides.

[0005] Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the *in vivo* experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

[0006] Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000-600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transiuminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG).

[0007] PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000-300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

[0008] The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

[0009] Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified:

[0010] In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80-90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining

SMC in the contractile phenotypic state.

[0011] Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i. e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/ migration usually begins within 1-2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture,* Campbell, J.H. and Campbell, G.R., Eds, CRC Press, Boca Ration, 1987, pp. 39-55) ; Clowes, A.W. and Schwartz,. S.M., Circ. Res. 56:139-145, 1985).

[0012] Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7-14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3-6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374-1387, 1989).

[0013] Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30-50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

Summary of the Invention:

Novel Features and Applications to Stent Technology

[0014] Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

[0015] In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

[0016] An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

[0017] One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

Description of the Drawings:

[0018] The invention will be better understood in connection with the following figures in which Figures 1 and 1A are top views and section views of a stent containing reservoirs as described in the present invention;

Figures 2a and 2b are similar views of an alternate embodiment of the stent with open ends;

Figures 3a and 3b are further alternate figures of a device containing a grooved reservoir; and

Figure 4 is a layout view of a device containing a reservoir as in Figure 3.

Detailed Description of the Invention

[0019] Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after an-

gioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127-132 (1991); Popma et al., 84 Circulation, 1426-1436 (1991)).

[0020] Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S.M. and Faxon, D.P., 4 Coronary Artery Disease, 232-242 (1993); Serruys, P.W. et al., 88 Circulation, (part 1) 1588-1601, (1993).

[0021] Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent 10 seen in layout in Figure 4, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496-501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412-422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

[0022] Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25-626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625-634, (1980); Clowes, A.W. and Clowes, M.M., 52 Lab. Invest., 611-616, (1985); Clowes, A.W. and Clowes, M.M., 58 Circ. Res., 839-845 (1986); Majesky et al., 61 Circ Res., 296-300, (1987); Snow et al., 137 Am. J. Pathol., 313-330 (1990); Okada, T. et al., 25 Neurosurgery, 92-898, (1989) colchicine (Currier, J.W. et al., 80 Circulation, 11-66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J.S. et al., 245 Science, 186-188 (1989), angiopeptin (Lundergan, C.F. et al., 17 Am. J. Cardiol. (Suppl. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Nati, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G.A.A., et al., 253 Science, 1129-1132 (1991), terbinafine (Nemecek, G.M. et al., 248 J. Pharmacol. Exp. Thera., 1167-11747 (1989), trapidil (Liu, M.W. et al., 81 Circulation, 1089-1093 (1990), interferon-gamma (Hansson, G.K. and Holm, 84 J. Circulation, 1266-1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510-518 (1992), see also Berk, B.C. et al., 17 J. Am. Coll. Cardiol., 111B-1 17B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

[0023] Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2- mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC *in vitro* while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277-2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409-1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

[0024] Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

[0025] Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

[0026] These can vary:

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.
- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.
- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.
- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e. g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.
- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake
- Extravascular delivery by the pericardial route
- Extravascular delivery by the advential application of sustained release formulations.

[0027] Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents
prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method - Delivery from Polymer Matrix:

[0028] Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolacton-glycolide,polyorthoesters, polyanhydrides; poly-aminoacids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly (hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

[0029] Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the. solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method - Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

[0030] Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt% to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outerlayer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method - Delivery via lysis of a Covalent Drug Tether

[0031] Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method - Pericardial Delivery

[0032] A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000p. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

[0033] B: Conformal coating: Rapamycin is combined with a polymer that has a melting temperature just above 37°C, range 40°-45°C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformally to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

[0034] As seen in the figures it is also possible to mod-

ify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in Figures Ia, 2a and 3a, any stent strut 10, 20, 30 can be modified to have a certain reservoir or channel 11, 21, 31. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. Figure 4 shows a stent 40 with a reservoir 45 created at the apex of a flexible strut. Of course, this reservoir 45 is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

[0035] In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

[0036] These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

Claims

1. A stent comprising:
   a generally thin walled cylinder, said cylinder containing a plurality of struts, said struts expandable dependent on the amount of force applied to said strut, and said struts having a generally uniform thickness; and a channel formed in at least one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a therapeutic agent applied therein.

2. A stent according to claim 1 wherein said channel has a generally rectangular perimeter.

3. A stent according to claim 2 wherein said therapeutic agent is rapamycin coated to said channel.

4. The stent of claim 3 wherein said channel is rectangular in shape.

5. The stent of claim 3 containing struts with said channels.

6. The stent of claim 3 wherein said channel is laser cut into said strut.

7. The stent of claim 1 wherein the therapeutic agent is rapamycin.

8. A stent comprising a generally thin walled structure containing a plurality of struts, the struts expandable to assume the shape of a lumen into which the stent is emplaced, said struts having a thickness, and a channel formed in at last one of said struts, said channel having a closed perimeter on all sides and an open top, and said channel smaller in all dimensions than said strut, said channel containing a therapeutic agent applied therein.

FIG. 1

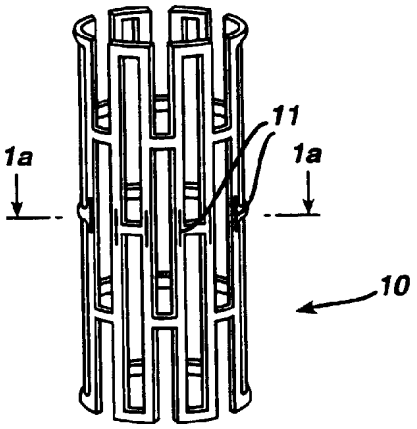


FIG. 1a

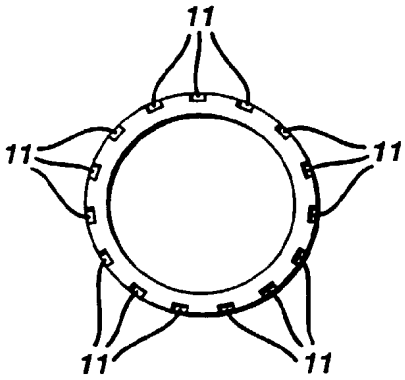


FIG. 2a

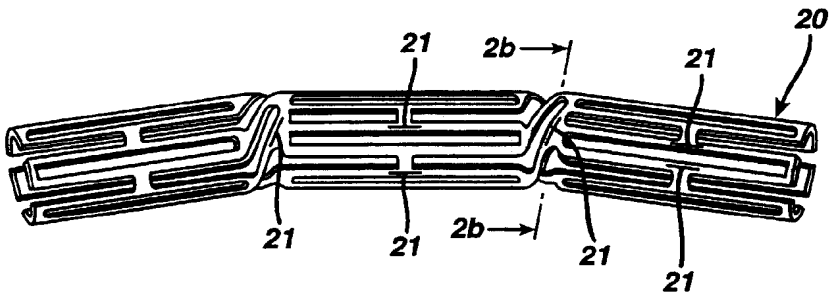


FIG. 2b

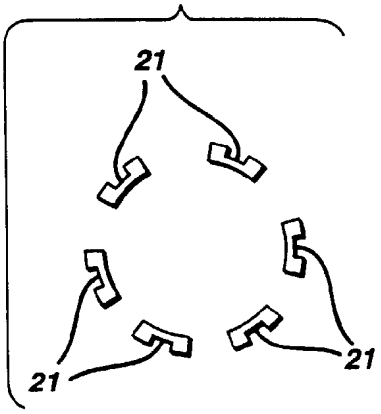


FIG. 3a

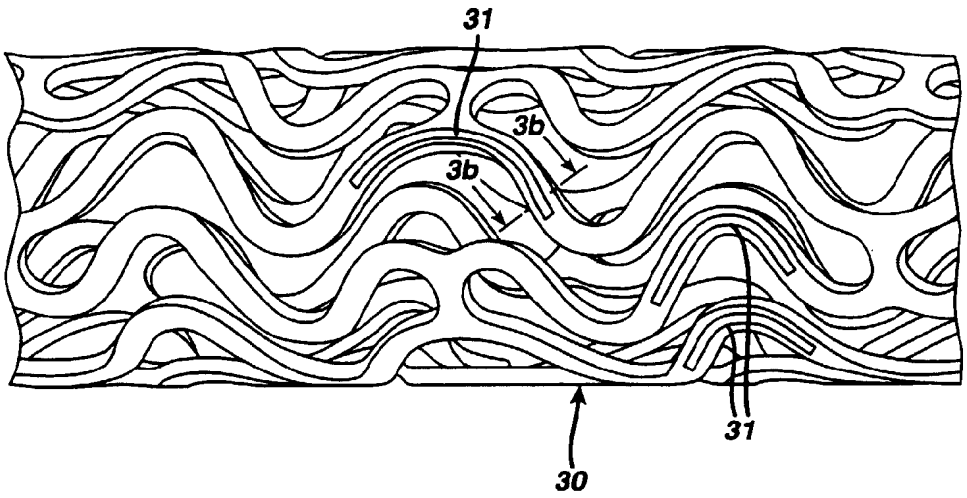


FIG. 3b

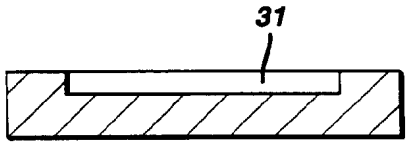
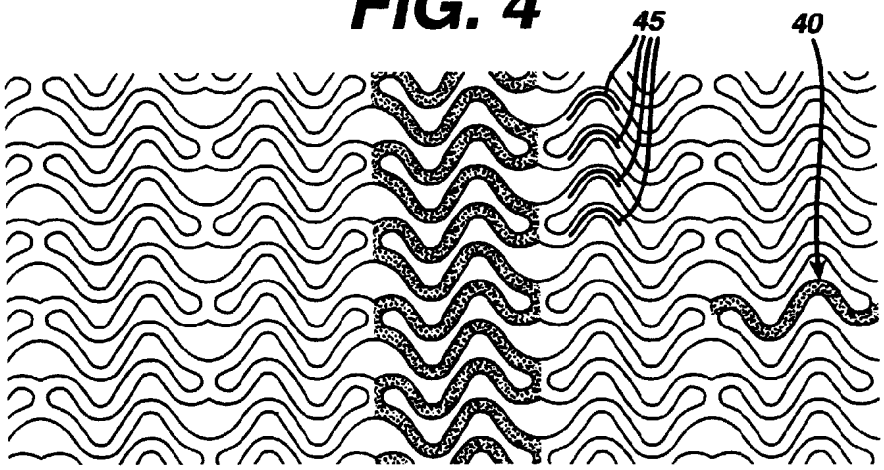


FIG. 4



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Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: MULTIPLE UNIT CONTROLLED FOOD EFFECT–INDEPENDENT RELEASE PHARMACEUTICAL PREPARATIONS AND METHOD FOR PREPARING THE SAME

(54) Bezeichnung: AGITATIONSUNABHÄNGIGE PHARMAZEUTISCHE MULTIPLE–UNIT–RETARDZUBEREITUNGEN UND VERFAHREN ZU IHRER HERSTELLUNG

(57) Abstract

The present invention relates to orally applicable multiple unit controlled–release dosage forms with controlled food effect–independent active substance release and to a method for producing the same using a selected erodible hydrophilic polymer (HPC) and limiting the maximum size of the substance–containing polymer particle to ≤3 mm.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft oral applizierbare Multiple–Unit–Retarddosisformen mit kontrollierter Agitations–unabhängiger Wirkstofffreisetzung und Verfahren zu ihrer Herstellung unter Verwendung eines ausgewählten erodierbaren hydrophilen Polymers (HPC) und Limitierung der Maximalgröße der Wirkstoff–enthaltenden Polymerpartikel auf ≤3 mm.

LEDIGLICH ZUR INFORMATION

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Agitationsunabhängige pharmazeutische Multiple-Unit-Retardzubereitungen und Verfahren zu ihrer Herstellung

Die vorliegende Erfindung betrifft oral applizierbare Multiple-Unit-Retarddosisformen mit kontrollierter und Agitations-unabhängiger Freisetzung und Verfahren zu ihrer Herstellung unter Verwendung eines ausgewählten erodierbaren hydrophilen Polymers.

Für viele Arzneimittel ist es wünschenswert, dass sie nach einmal täglicher Verabreichung eine kontrollierte, langanhaltende und gleichmäßige Freisetzung des Wirkstoffs gewährleisten. Auf diese Weise kann die gewünschte Plasmakonzentration ohne große Schwankungen über einen längeren Zeitraum aufrecht erhalten werden und somit die Arzneimittelsicherheit und die Patienten-Compliance erhöht werden. Formulierungen, die den Wirkstoff auf diese Weise über einen definierten Zeitraum freisetzen, werden als Retardformulierungen bezeichnet. Es sind bereits verschiedene Techniken zu ihrer Herstellung bekannt.

Sehr häufig werden für diesen Zweck Single-Unit-Matrixtabletten eingesetzt, die den Wirkstoff in einer Matrix aus Polymeren und einigen pharmazeutischen Hilfsstoffen enthalten. Das Polymer kann entweder hydrophil oder hydrophob sein oder eine Mischung daraus darstellen. Mittlerweile sind Matrixtabletten mit hydrophilen Polymeren sehr beliebt geworden, da diese vergleichsweise preiswert, nichttoxisch, auf herkömmlichen Anlagen verarbeitbar sind, usw.

Eine weitere Methode ist das Ummanteln von Zubereitungsformen mit gepufferten bzw. pH-abhängigen Umhüllungen, die eine kontrollierte Freisetzung in bestimmten Bereichen des Magen-Darm-Traktes gewährleisten soll.

Während die Erosions-Matrixtabletten anfällig sind gegenüber mechanischer Beanspruchung, insbesondere hydrodynamischen Belastungen, sind die pH-gesteuerten

Formulierungen anfällig gegenüber pH-Wert-Änderungen im Magen-Darm-Trakt. Während sich die Tablette durch den Magen-Darm-Trakt bewegt, variiert sowohl der pH-Wert, als auch die mechanische Beanspruchung, insbesondere auch in Abhängigkeit von Art und Menge der Füllung des Magens und des Verdauungstraktes. Diese Abhängigkeit der Wirkstofffreisetzung wird als „Agitationsabhängigkeit" oder als „Food-Effekt" bezeichnet. Es zeigt sich, dass die Freisetzungsrate der meisten Retardformulierungen abhängig ist von der Nahrungsaufnahme und somit unterschiedliche Wirkprofile auftreten in Abhängigkeit davon, ob die Einnahme des Arzneimittels vor, während oder nach einer Mahlzeit erfolgt.

Es gibt zahlreiche Versuche die unerwünschte Variabilität dieses „Food-Effekts" auszuschalten bzw. zu minimieren. Für erosionskontrollierte Zubereitungen wurde ein annähernd agitationsunabhängiges Single-Unit-System beschrieben, das jedoch technisch sehr aufwendig und daher inpraktikabel ist (vgl. W.D. Lindner et al. Farm., 51 (1996) 263). Als weitere Möglichkeit einer agitationsunabhängigen Zubereitung wurde ein Single-Unit-osmotisches Pumpsystem beschrieben und teilweise erfolgreich vermarktet. Hierbei wird der Wirkstoff durch definierte Öffnungen oder Poren einer Kammer nach außen gepreßt, wobei der Preßdruck durch ein quellendes Polymer erzeugt wird, dessen Wasseraufnahme osmotisch gesteuert wird (vgl. US-Pat 4 449 983, US-Pat 4 203 400 und US-Pat 4 327 725).

Die Probleme und Nachteile der bisher vorgeschlagenen und eingesetzten agitationsunabhängigen Retardformulierungen sind bekannt und unter anderem in der Beschreibung von EP 0 425 298.A2 dargelegt. Gemäß dieser Anmeldung wird versucht die Agitationsunabhängigkeit von salzbildenden Wirkstoffen durch unterschiedliches Ummanteln mit schwerlöslichen Polymeren zu erreichen. Die Nachteile dieses Verfahrens liegen ebenfalls in den technisch aufwendigen Verfahrensmaßnahmen und in der Tatsache, dass nur bestimmte salzbildende und somit leicht lösliche Wirkstoffe eingesetzt werden können.

Als Multiple-Unit-Formulierung werden solche Formulierungen bezeichnet, die im Gegensatz zu sogenannten Single-Unit-Formulierungen wie Tabletten aus mehreren kleinen Partikeln wie z.B. Pellets, Granulaten, Minitabletten oder Körnern bestehen, die z.B. in einer Kapsel enthalten sind. Im Magen-Darm-Trakt liegen diese Partikel dann unabhängig voneinander vor. Solche Multiple-Unit-Formulierungen weisen eine Reihe von Vorteilen im Vergleich zu Single-Unit-Formulierungen auf. Sie sorgen für eine gleichmäßigere Absorption des Wirkstoffs und für geringere inter- und intraindividuelle Schwankungen der pharmacokinetischen Profile. Weiterhin lassen sich so in einfacher Weise verschiedene Wirkstoffe und Dosierungen z.B. in Kapseln einbringen. Diese Formulierungen können so den unterschiedlichen medizinischen Anforderungen ohne großen Aufwand angepaßt werden.

Die Aufgabe der vorliegenden Erfindung ist darin zu sehen, agitationsunabhängige Multiple-Unit-Retardformulierungen, d.h. Formulierungen ohne störenden Food-Effekt für alle Arten von Wirkstoffen, insbesondere für schwerlösliche Wirkstoffe zur Verfügung zu stellen, die in einfacher Weise hergestellt werden können.

Multiple-Unit-Retardformulierungen gemäß der vorliegenden Erfindung sind Formulierungen, die im USP Paddletest mit Apparat II 80 % des Wirkstoffs innerhalb von 4 bis 14 Stunden, vorzugsweise innerhalb von 6 bis 12 Stunden freisetzen, bezogen auf die gesamte Wirkstoffmenge in der Formulierung.

Agitationsunabhängig gemäß der vorliegenden Erfindung sind Formulierungen, die im USP XXII Paddletest mit 900 ml Freisetzungsmedium, pH 6,8 bei einer Rührgeschwindigkeit von 50 UpM und von 150 UpM eine maximale Freisetzungsdifferenz von $\pm$ 10 %, vorzugsweise $\pm$ 5 % aufweisen.

Die Rührgeschwindigkeit des Paddletests nach USP wurden ausgewählt im Hinblick auf die Publikation B. Abrahamsson et al., Eur. J. Pharm. Sci., 46 (1998) 69, wonach die mechanische Beanspruchung einer Tablette im Magen-Darm-Trakt etwa mit den

Bedingungen zu vergleichen ist, die einer Rührbewegung im Paddletest mit bis ca. 150 U/min entsprechen.

Diese Aufgabe läßt sich erfindungsgemäß dadurch lösen, dass man

a) als hydrophiles Polymer Hydroxypropylcellulose (HPC) mit einem mittleren Molekulargewicht von 250 000 bis 1 200 000, vorzugsweise 350 000 bis 1 150 000 in einer Menge von 40 bis 95 Gew.-%, vorzugsweise 45 bis 90 Gew.-%, bezogen auf das Wirkstoff-Polymergemisch, und einem molaren Substitutionsgrad von $\geq$3 als retardierendes Erosionsmaterial einsetzt und

b) die Wirkstoff-Polymer-Kombination in kleine Partikel wie Pellets, Granulate oder Minitabletten mit einem maximalen Durchmesser von 0,2 bis 3,0 mm, vorzugsweise von 0,5 bis 2 mm, überführt,

Es kann auch HPC mit einem mittleren Molekulargewicht von 700 000 bis 1 200 000, vorzugsweise 850 000 bis 1 150 000 eingesetzt werden.

Unter maximalem Durchmesser wird hierbei die größte Längenausdehnung des Partikels verstanden; sie liegt erfindungsgemäß bei 0,2 bis 3 mm.

Gewünschtenfalls können die Minipartikel lackiert werden und auch weitere übliche pharmazeutische Hilfsstoffe hinzufügt werden.

Diese retardierten Minipartikel können in einfacher Weise in den gewünschten Dosiseinheiten als Multiple-Unit-Retarddosisformen hergestellt und verabreicht werden, wie z.B. in Hardgelatinekapseln, als Sachets oder zu Tabletten umgearbeitet werden, die unmittelbar nach Verabreichung wieder in die Minipartikel zerfallen und sich somit wie eine Multiple-Unit-Dosisform verhalten.

Bei Kenntnis des Standes der Technik war es nicht naheliegend, dass durch die Auswahl des oben genannten erodierbaren hydrophilen Polymers HPC und gleichzeitiger Limitierung der Maximalgröße der Wirkstoff-enthaltenden Polymerpartikel auf höchstens 3 mm Durchmesser eine agitationsunabhängige Retardformulierung hergestellt werden kann. Es war vielmehr zu erwarten, dass gerade leicht erodierbare hydrophile Polymere einen besonders starken Agitationseffekt bzw. Foodeffekt zeigen würden. Es ist z.B. bekannt, dass Nifedipin-enthaltende Matrixtabletten mit Durchmessern von 9 oder 10 mm, die HPC oder HPMC (Hydroxypropylmethylcellulose) als hydrophiles Polymer enthalten, stark agitationsabhängig sind und einen starken Food-Effekt zeigen. (Vgl. Adalat CC®; EP 0 299 211 und B. Abrahamsson et al, J. Controlled Rel., 52 (1998) 301).

Andererseits sind auch Minitabletten zur oralen Anwendung seit einiger Zeit bekannt und beschrieben (vgl. Colombo et al., Acta Technol. Legis. med. 1992, 3 (3), 137). Es ist aber bisher nicht bekannt, dass die erfindungsgemäßen Partikel mit einem maximalem Durchmesser von 3 mm agitationsunabhängige Retardformulierungen darstellen.

Zur Lösung der erfindungsgemäßen Aufgabe ist die Kombination beider Elemente a) und b) erforderlich. Eigene Versuche mit Minierosionstabletten, welche als Wirkstoff Nifedipin enthalten, die zwar einem Durchmesser von 2 mm besitzen, aber als erodierbares Polymer eine Mischung aus Hydroxyethylcellulose (HEC) und Hydroxyproylmethylcellulose (HPMC) enthalten, zeigen eine signifikante Agitationsabhängigkeit.

Überraschenderweise wurde gefunden, dass durch die Kombination der Auswahl des erodierbaren hydrophilen Polymers HPC und die Reduzierung der Größe der einzusetzenden Minipartikel auf maximal 3 mm Durchmesser in einfacher und effektiver Weise agitationsunabhängige Multiple-Unit-Retardformulierungen erhalten werden können.

Nach orientierenden Tests zeigten die erfindungsgemäßen Formulierungen praktisch keine Nahrungsmittelabhängigkeit.

Die Herstellung der erfindungsgemäß einzusetzenden Pellets, Granulate, Minitabletten oder Körner erfolgt nach üblichen Methoden. Neben den herkömmlichen Formulierungsmethoden, in denen HPC mit dem Wirkstoff und gegebenenfalls weiteren Hilfsstoffen unter Verwendung von Wasser oder organischen Lösungsmitteln granuliert wird, kann auch die Verwendung von Schmelzextrusionsmethoden in vorteilhafter Weise eingesetzt werden. Solche Schmelzextrusionsmethoden sind seit langem bekannt. Variationen dieser Schmelzextrusion werden auch in der jüngeren Patentliteratur vorgeschlagen (vgl. DE 195 04 831.8, EP 240 904, US-PS 5 456 923, EP 544 144 und insbesondere WO 96/25149).

Viele der bisher bekannten Methoden der Schmelzextrusion weisen gegenüber den erfindungsgemäß einsetzbaren Methoden eine Reihe von Nachteilen auf. So werden zur Herstellung eines Extrudates häufig mindestens zwei Polymere, z.B. ein wasserlösliches und ein wasserunlösliches verwendet. Durch die Notwendigkeit von zusätzlichen Weichmachern oder anderen Hilfsstoffen kann das Verhältnis Hilfsstoff/Arzneistoff ungünstig beeinflußt werden, so dass das fertige Produkt sehr voluminös und auch teuer ist. Gemäß der vorliegenden Erfindung können die agitations- und nahrungsunabhängigen Formulierungen bereits durch einfaches Mischen und Extrudieren des gewünschten Wirkstoffs mit HPC erhalten werden.

Gewünschtenfalls können natürlich auch für die erfindungsgemäßen Multiple-Unit-Retard-Formulierungen weitere Hilfsstoffe eingesetzt werden wie z.B. Magnesiumstearat oder Filmüberzüge oder Lackierungen, die das Aneinanderkleben der Partikel verhindern. Diese Hilfsstoffe haben jedoch keinen direkten Einfluß auf die agitationsunabhängige oder keinen Food-Effekt aufweisende Retardwirkung der erfindungsgemäßen Zubereitung.

Es ist auch möglich, für die Herstellung der Minitabletten neben dem wesentlichen Polymer HPC weitere hydrophile und wasserunlösliche Polymere wie z.B. Polymethacrylatester einzusetzen. Ein Beispiel ist das bekannte Ammonio Methacrylat Copolymer Typ B (Eudragit® RS PO).

Gegenstand der vorliegenden Erfindung sind auch Verfahren zur Herstellung von Multiple-Unit-Retarddosisformen, dadurch gekennzeichnet, dass mindestens ein therapeutisch wirksamer Stoff und HPC mit einerm mittleren MG von 250 000 bis 1 200 000 als hydrophiles thermoplastisches, aber pharmazeutisch unbedenkliches Polymer sowie gegebenenfalls weitere übliche pharmazeutische Hilfsstoffe, die jedoch nicht zum Retardeffekt beitragen, gemischt, granuliert und tablettiert oder gemischt, extrudiert und granuliert werden zu Partikeln mit einem maximalen Teilchendurchmesser von 3 mm und diese dann in eine geeignete orale Applikationsform überführt werden.

Beim Extrusionsverfahren werden therapeutisch wirksame Arzneistoffe und das Polymer entweder gleichzeitig, ohne vorheriges Mischen, oder als Mischung, nach vorherigem Mischen, in einem normalen Extruder, bevorzugterweise einem Doppelschneckenextruder, gefördert, welcher vorher auf eine Temperatur erhitzt wurde, bei der das Polymer und der Arzneistoff nicht abgebaut werden. Hierbei beträgt der Temperaturbereich an der Austrittsdüse des Extruders 50 bis 220°C, vorzugsweise 80 bis 210°C und besonders 100-180°C. Im Bereich des Produkteintritts in den Extruder beträgt die Temperatur um 25°C. Die Temperatur im Zwischenbereich des Extruders liegt zwischen der Temperatur im Produkteintrittsbereich des Extruders und der Temperatur an der Austrittsdüse des Extruders.

Die homogene Mischung erweicht während des Durchlaufs durch den Extruder und wird am Ende durch eine Platte, die mindestens eine Düse mit einem definierten Durchmesser von ca. 0,2 bis 3,0 mm, vorzugsweise von 0,5 bis 2,0 mm enthält,

gepreßt. Die extrudierten Stränge, die beim Austritt aus der Extruderdüse noch weich sind und bei Raumtemperatur schnell fest werden, werden unmittelbar nach ihrem Austritt zu Granulat mit einem Teilchendurchmesser von ca. 0,2 bis 3 mm, vorzugsweise 0,5 bis 2 mm, geschnitten. Alternativ werden die extrudierten Stränge sofort (on-line) granuliert (z.B. Wasser-Ring-Granulation oder Unterwasser-Granulation oder Luft-Granulation) oder sofort in Stücke geschnitten. Bevorzugt ist die Luftgranulation. Die erhaltenen Extrudate können direkt in Hartgelatinekapseln gefüllt werden. Als besondere Ausführungsform hat es sich als vorteilhaft erwiesen, die erhaltenen Extrudate vor ihrer Einfüllung in Gelatinekapseln noch zu lackieren, vorzugsweise mit einem wasserunlöslichen aber wasserdurchlässigen und nicht gelbildenden Polymer.

Diese Retarddosisform gemäß der vorliegenden Erfindung ist nicht anfällig gegenüber mechanischer Beanspruchung bzw. hydrodynamischer Belastung im Magen-Darm-Trakt; die Rate der Wirkstofffreisetzung hängt daher nicht von der mechanischen Beanspruchung und der hydrodynamischen Belastung ab, der das Produkt ausgesetzt ist und ist unabhängig vom Füllungsgrad des Magens. Die Retarddosisform weist also keinen Food-Effekt auf.

Die lackierten Extrudate können mit konventionellen Hilfsstoffen (z.B. mikrokristalliner Cellulose, Ac-Di-Sol® usw.) zu Tabletten verpreßt werden. Diese Tabletten zerfallen rasch nach ihrer Verabreichung, so dass sich die Tablette wie eine Multi-Unit-Dosisform verhält.

Die Formulierung gemäß der vorliegenden Erfindung kann auch mit bekannten Tablettierungsprozessen hergestellt werden, bei denen die Inhaltsstoffe z.B. in bekannter Weise granuliert, gleitfähig gemacht und zu Mikrotabletten von einem Durchmesser $\leq$3 mm, vorzugsweise $\leq$2 mm komprimiert werden.

Die agitationsunabhängige Retardierung wird, wie bereits erwähnt, im Gegensatz zu den Formulierungen nach dem Stand der Technik bei der vorliegenden Erfindung durch die Kombination a) des verwendeten Polymers HPC und b) den maximalen Durchmesser erreicht, während die Beschichtung lediglich dazu dient, die Dosisform vor dem Verkleben zu schützen.

Bei dem zu verwendenden Wirkstoff kann es sich um beliebige oral zu verabreichende Arzneistoffe handeln, wie z.B. Antiinfektiva, Kreislaufmittel, Antimykotika, Antidepressiva, Antidementika, Antiepileptika, Antiphlogistika, Analgetika, Antiasthmatika, Antithrombotika Antitumormittel, Antimalariamittel, nichtsteroidale entzündungshemmende Mittel (NSAID), Diuretika, Antiarrhythmica, blutzuckersenkende Mittel, ACE-Hemmer, Sedativa, Decongestiva, Antihistaminika oder Lipidsenker. Lipidsenker können unter anderem Apo B-Inhibitoren oder MTP-Inhibitoren sein. Von besonderem Interesse sind die Apo B-Inhibitoren gemäß EP 705 831, auf die hier ausdrücklich Bezug genommen wird. Von ganz besonderem Interesse ist die Substanz 2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-yl-methyl)-phenyl]-*N*-(2-hydroxy-1-phenyl-ethyl)acetamid. Für die Zwecke der vorliegenden Erfindung werden nur diejenigen Arzneistoffe eingearbeitet, die sich unter den Temperaturen und Verarbeitungsbedingungen nicht zersetzen. Die zu verabreichende Wirkstoff-menge pro Dosiseinheit kann je nach Art des Arzneistoffs und der Freisetzungsrate innerhalb weiter Grenzen variiert werden. Es hat sich als vorteilhaft erwiesen, auf einen Gew.-Teil Wirkstoff 0,8 bis 10 Gew.-Teile, vorzugsweise 1 bis 5 Gew.-Teile, des gelbildenden Polymers einzusetzen.

Im Gegensatz zu den bisher bekannten Techniken wird zur Retardation gemäß der vorliegenden Erfindung nur ein einziges Polymer benötigt. Die gewünschte Freisetzungsrate erhält man durch Variation der Herstellungsparameter. Die Arzneistoffreisetzungsrate wird z.B. beeinflußt durch die Arzneistoffkonzentration im Endprodukt oder durch Verfahrensparameter der Extrusion, wie die Schneckengeometrie,

die Extrusionsrate, die Extrusionstemperatur, der Durchmesser und die Oberfläche des Extrudats, die Viskosität und Molekulargewicht des Polymeren, usw.

Wie bereits erwähnt können auch weitere übliche Hilfsstoffe verwendet werden, die bei der Herstellung von festen Dosisformen in der Pharmazie üblich und aus der Literatur bekannt sind. Keiner dieser Hilfsstoffe ist jedoch notwendig um die erfindungsgemäß gewünschte Verzögerung der Freisetzung des Arzneistoffs und die Agitationsunabhängigkeit wesentlich zu beeinflussen. Diese Hilfsstoffe dienen vielmehr nur dazu, das Verfahren flexibler zu machen.

Man lackiert die Extrudate oder Minitabletten gegebenenfalls z.B. mit pH-unabhängigen wäßrigen Dispersionen wie einer Ethylcellulose-Dispersion (z.B. Aquacoat EC 30 Trademark of FMC) oder einem Poly(ethylacrylat, -methylmethacrylat) 2:1 (z.B. Eudragit NE 30 D Trademark of Röhm Pharma). Außerdem kann ein Weichmacher wie z.B. Triethylcitrat oder Tween 20 verwendet werden, damit der Lackfilm bei der Lagerung nicht spröde wird. In die Lacksuspension kann zusätzlich Magnesiumstearat als Antiklebmittel eingearbeitet werden. HPMC dient als Porenbildner. Der Lack hat im wesentlichen keinen Einfluß auf die Freisetzungsrate, ausgenommen, dass es während der ersten 1-2 Stunden nach der Verabreichung zu einer Verzögerung des Einsetzens der Freisetzung kommen kann (Lag-Zeit).

Als typische Lacksuspensionen für Minitabletten und Extrudate seien genannt:
(Alle Angaben in Gew.-%)

A. 30 - 60 % (bevorzugt 40 %) Eudragit® NE 30 D Dispersion; 3 - 10 % (bevorzugt 5 %) HPMC 3 cP; 0,05 - 0,5 % (bevorzugt 0,1 %) Tween 20; 1 - 7,5 % (bevorzugt 2,5 %) Magnesiumstearat und vollentsalztes Wasser bis 100 %.

B. 15 - 30 % (bevorzugt 25 %) Aquacoat® EC 30 D Dispersion; 3 - 10 % (bevorzugt 4 - 5 %) HPMC 15 cP; 0,5 - 4 % (bevorzugt 2 %) Triethylcitrat und vollentsalztes Wasser bis 100 %.

Die Lacksuspensionen z.B. werden hergestellt, indem man zunächst HPMC und den Weichmacher getrennt in Wasser löst und dann mit der Dispersion des Filmbildners mischt. Bei Anwesenheit von Magnesiumstearat wird dieses vor der Zugabe der Eudragit-NE-30-D-Dispersion in der wäßrigen Lösung von HPMC und Weichmacher dispergiert.

Die gegebenenfalls lackierten Partikel der erfindungsgemäßen Wirkstoff-Polymerkombination wie Pellets, Granulate, Minitabletten oder Körner können nach üblichen Methoden in Kapseln gefüllt, zu Tabletten gepreßt oder zu sonstigen bekannten Verabreichungsformen oder Fertigarzneimitteln weiterverarbeitet werden.

Die Erfindung wird anhand der nachfolgenden Beispiele näher erläutert.

Einfluß der Paddle-Apitation auf die Wirkstoffreisetzung

Die Wirkstofffreisetzung aus den erfindungsgemäßen Beispielen 16 und 17 sowie aus dem Vergleichsbeispiel A über die Zeit wurde in einem USP XXII-Paddle-Test untersucht. Dabei zeigte sich, dass bei den Beispielen 16 und 17 die Wirkstoff-freisetzung bei 50 und 150 Umdrehungen pro Minute (UpM) über einen Zeitraum von 14 Stunden (also bis zur vollständigen Freisetzung) ummaximal 5 % auseinanderlag, während beim Vergleichsbeispiel A Freisetzungs-differenzen von bis zu 50 % auftraten.

Vergleichsbeispiel A

19,4 Gew. Teile Hydroxypropylmethylcellulose (Viskosität 100 000 cP, Typ 2208) und 45,3 Gew.- Teile Hydroxyethylcellulose (Viskosität 15 000 cP) werden mit einer wäßrigen Suspension von Nifedipin (30 Gew.-Teile) und Hydroxypropylcellulose (2 Gew.-Teile) einer Viskosität <10 cP granuliert. Das erhaltene Granulat wird mit Magnesiumstearat gleitfähig gemacht und zu 2 mm Minitabletten von 6,4 mg komprimiert. Die Minitabletten werden auf herkömmliche Weise mit einer wäßrigen Dispersion von Eudragit NE 30 D, Magnesiumstearat, Tween 20®, Hydroxypropylmethylcellulose 3 cP und Wasser lackiert. Pro kg Minitabletten werden 0,6 kg Lacksuspension A aufgesprüht. Einige lackierte Minitabletten mit einem Äquivalent von 30 mg Nifedipin werden verkapselt.

Ausführungsbeispiele

Beispiel 1

3 kg des Arzneistoffs Nifedipin werden mit 7 kg hochviskosem HPC (MG 400 000 von Nippon Soda, Japan) gemischt. Die Mischung wird auf einem Doppelschneckenextruder mit zwei Austrittsdüsen mit einem Durchmesser von 2 mm verarbeitet. Das Material wird bei einer Düsentemperatur von 150°C extrudiert. Die Temperatur der verschiedenen Untereinheiten im Extruderzylinder wird auf eine Temperatur eingestellt, die mindestens etwa 10°C unter der Düsentemperatur liegt. Das Extrudat wird in etwa 2 mm lange Zylinder geschnitten und in einer Wirbelschichtlackieranlage lackiert. Pro kg Extrudat werden 0,6 kg der Lacksuspension A aufgesprüht. Die Lackierung erfolgt unter üblichen Bedingungen.

Beispiel 2

Analog Beispiel 1, jedoch werden 2 kg Nifedipin mit 8 kg des gleichen Polymertyps gemischt.

Beispiel 3

Analog Beispiel 1, jedoch beträgt die Düsentemperatur 160°C.

Beispiel 4

Analog Beispiel 1, jedoch beträgt der Düsendurchmesser 1, 4 mm.

Beispiel 5

Analog Beispiel 1, jedoch beträgt der Düsendurchmesser 0,8 mm.

Beispiel 6

Analog Beispiel 1, jedoch wurden die extrudierten Stränge zunächst in etwa 3 mm lange Zylinder geschnitten.

Beispiel 7

Analog Beispiel 1, jedoch wurden die etwa 2 mm langen geschnittenen Zylinder nicht lackiert.

Beispiel 8

Analog Beispiel 1, jedoch beträgt die Düsentemperatur 140°C.

Beispiel 9

Analog Beispiel 1, jedoch wird als Polymer HPC mit einem mittleren Molekulargewicht von ca. 850 000 (Fa. Hercules, USA) verwendet.

Beispiel 10

Analog Beispiel 1, jedoch wird als Polymer HPC mit einem mittleren Molekulargewicht von ca. 1 000 000 (Fa. Hercules, USA) verwendet.

Beispiel 11

Analog Beispiel 1, jedoch wird als Arzneistoff Nisoldipin verwendet.

Beispiel 12

Analog Beispiel 1, jedoch wird als Arzneistoff Nimodipin verwendet, HPC (MG 400 000, Nippon Soda, Japan) eingesetzt, und die Düsentemperatur beträgt 110°C.

Beispiel 13

Die gleiche Zusammensetzung wie in Beispiel 1 wird in einer kommerziell erhältlichen Extrusions- und Granulationsvorrichtung unter den gleichen Extrusionsbedingungen extrudiert und dann durch das Wasser-Ring-Verfahren sofort granuliert und getrocknet. Die entstandenen Extrudate waren leicht gerundet und dadurch besser verarbeitbar.

Beispiel 14

Die gleiche Zusammensetzung wie in Beispiel 1 wird in einer kommerziell erhältlichen Extrusionsvorrichtung extrudiert mit einer Düsenplatte 40 x 0,8 mm oder 36 x 1,3 mm Bohrungen, und dann durch Luft-Granulation sofort on-line granuliert und getrocknet. Die entstandenen Extrudate waren besser verarbeitbar. Die Granulate wurden wie in Beispiel 1 lackiert.

Beispiel 15

Die gleiche Zusammensetzung wie in Beispiel 1 wird durch einen Extruder mit Austrittdüsen mit einem Durchmesser von 1 mm extrudiert, der extrudierte Strang durch

Besprühen mit Wasser gekühlt und sofort granuliert und getrocknet. Die erhaltenen Extrudate werden wie in Beispiel 1 beschrieben, weiterverarbeitet.

Beispiel 16

250 Teile (Gew.) Hydroxypropylcellulose (MG 1 000 000; Viskosität 1 500 bis 3 000 cP (1 % w/v; 25°C)) werden mit einer wäßrigen Suspension von Nifedipin (30 Teile) und Hydroxypropylcellulose (2 Teile) einer Viskosität <10 cP granuliert. Das erhaltene Granulat wird mit Magnesiumstearat (1,5 Teile) gleitfähig gemacht und zu 2 mm-Minitabletten von 6,5 mg komprimiert. Die Minitabletten werden auf herkömmliche Weise mit einer wäßrigen Dispersion von Eudragit NE 30 D, Magnesiumstearat, Tween 20®, Hydroxypropylmethylcellulose 3 cP und Wasser lackiert. Pro kg Minitabletten werden 0,6 kg Lacksuspension A aufgesprüht. Einige lackierte Minitabletten mit einem Äquivalent von 30 mg Nifedipin werden verkapselt.

Beispiel 17

Hydroxypropylcellulose entsprechend Beispiel 16 (42,6 Teile) wird mit Eudragit® RS PO (40,8 Teile) vermischt und mit einer wäßrigen Suspension von Nifedipin (30 Teile) und Hydroxypropylcellulose (2 Teile) einer Viskosität <10 cP granuliert. Das erhaltene Granulat wird mit Magnesiumstearat (1,5 Teile) gleitfähig gemacht und zu 2 mm-Minitabletten von 6,5 mg komprimiert. Die Minitabletten (2 mm Durchmesser) werden analog Beispiel 16 lackiert.

Beispiel 18

1 kg 2-Cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3-b]indol-9-yl-methyl)-phenyl]-*N*-(2-hydroxy-1-phenyl-ethyl)acetamid werden mit 2 kg HPC (MG 250 000-400 000, Nippon Soda, Japan) gemischt. Die Mischung wird auf einem Doppelschneckenextruder mit zwei Austrittdüsen mit einem Durchmesser von 2 mm

verarbeitet. Das Material wird bei einer Düsentemperatur von 215°C extrudiert. Das Extrudat wird in etwa 2 mm lange Zylinder geschnitten und in einer Wirbelschichtlackieranlage analog Beispiel 1 lackiert.

Falls nicht ausdrücklich anders angegeben, soll der Begriff „Teile" in der vorliegenden Anmeldung immer als „Gew.-Teile" verstanden werden.

Patentansprüche

1. Verfahren zur Herstellung einer oral applizierbaren Multiple-Unit-Retarddosisformulierung mit kontrollierter Agitations-unabhängiger Freisetzung, dadurch gekennzeichnet, dass man den hydrophilen Polymer HPC mit einem mittleren Molekulargewicht von 250 000 bis 1 200 000 in einer Menge von 40 bis 95 Gew.-%, bezogen auf das Wirkstoff-Polymergemisch und einem molaren Substitutionsgrad von mindestens 3 als retardierendes Erosionsmaterial mit mindestens einem pharmazeutischen Wirkstoff kombiniert und diese Wirkstoff-Polymerkombination in kleine Partikel mit einem Durchmesser von 0,2 bis 3,0 mm überführt und diese bei der Herstellung von wirksamen oralen Applikationsformen und Fertigarzneimittel verwendet.

2. Verfahren zur Herstellung einer Formulierung gemäß Anspruch 1, dadurch gekennzeichnet, dass man HPC in einer Menge von 45 bis 90 Gew.-% einsetzt.

3. Verfahren zur Herstellung einer Formulierung gemäß Anspruch 1, dadurch gekennzeichnet, dass man HPC mit einem mittleren Molekulargewicht von 350 000 bis 1 150 000 einsetzt.

4. Verfahren zur Herstellung einer Formulierung gemäß Anspruch 1, dadurch gekennzeichnet, dass man die Wirkstoff-Polymerkombination in kleine Partikel mit einem maximalen Durchmesser von 0,5 bis 2 mm überführt.

5. Verfahren zur Herstellung von Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, dass man die Partikel der Wirkstoff-Polymerkombination durch Schmelzextrusion und Granulation herstellt.

6. Verfahren zur Herstellung von Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, dass man die Partikel der Wirkstoff-Polymerkombination durch herkömmliche Tablettierungsmethoden herstellt.

7. Verfahren zur Herstellung von Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, dass man die Wirkstoff-Polymerkombinationspartikel in Form von Pellets, Granulaten, Minitabletten oder Körnern herstellt und diese in einer wirksamen Dosierung in Kapseln füllt.

8. Verfahren zur Herstellung von Formulierungen gemäß Anspruch 1, dadurch gekennzeichnet, dass man die Wirkstoff-Polymerkombinationspartikel zusätzlich lackiert.

9. Verwendung von HPC mit einem mittleren Molekulargewicht von 250 000 bis 1 200 000 bei der Herstellung von Agitations-unabhängigen pharmazeutischen Retard-Zubereitungen, erhältlich gemäß Anspruch 1.

10. Verwendung von HPC mit einem mittleren Molekulargewicht von 350 000 bis 1 150 000 als wesentlichem Retardierungspolymer und gegebenenfalls geringer Mengen weiterer hydrophiler Polymere wie Polymethacrylester bei der Herstellung von Agitations-unabhängigen Retard-Zubereitungen gemäß Anspruch 1.

11. Verwendung von Wirkstoff-Polymerkombinationspartikeln gemäß Anspruch 1 zur Herstellung von Fertigarzneimitteln in Form von Kapseln oder Tabletten.

12. Oral applizierbare Multiple-Unit-Retarddosisformulierungen mit kontrollierter Agitations-unabhängiger Freisetzung erhältlich gemäß Anspruch 1.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/06882

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16

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 7 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.
X	EP 0 205 282 A (EUROCELTIQUE) 17 December 1986 (1986-12-17) claims 1,8,14 column 2, line 19 - line 30 examples 1-7	1,3-6, 8-12
A	ACQUIER, R., ET AL.: "Hydroxypropyl cellulose et liberation des principes actifs I. Influence de la masse moleculaire du polymere et de sa concentration" S.T.P PHARMA SCIENCES, vol. 2, no. 6, 1992, pages 469-474, XP000865524 the whole document	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2000	31/01/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/06882

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ACQUIER, R.; ET AL.: "Approche du comportement des hydroxypropylcelluloses en presence d'eau, en fonction de la masse moleculaire et de la concentration" PHARMACEUTICA ACTA HELVETIAE, vol. 67, no. 11, 1992, pages 315-320, XP000863695 Bern, CH the whole document	1-12

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INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...onal Application No
PCT/EP 99/06882

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 205282 A	17-12-1986	AT 127687 T	15-09-1995
		AU 595801 B	12-04-1990
		AU 5828486 A	18-12-1986
		CA 1277913 A	18-12-1990
		DE 3650390 D	19-10-1995
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		NO 862287 A,B,	12-12-1986
		PT 82746 A,B	01-07-1986
		US 4940587 A	10-07-1990

INTERNATIONALER RECHERCHENBERICHT

Inte onales Aktenzeichen
PCT/EP 99/06882

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 A61K9/16

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 A61K

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP 0 205 282 A (EUROCELTIQUE) 17. Dezember 1986 (1986-12-17) Ansprüche 1,8,14 Spalte 2, Zeile 19 - Zeile 30 Beispiele 1-7	1,3-6, 8-12

A	ACQUIER, R., ET AL.: "Hydroxypropyl cellulose et liberation des principes actifs I. Influence de la masse moleculaire du polymere et de sa concentration" S.T.P PHARMA SCIENCES, Bd. 2, Nr. 6, 1992, Seiten 469-474, XP000865524 das ganze Dokument	1-12

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[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

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Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
19. Januar 2000	31/01/2000

Name und Postanschrift der Internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

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INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen
PCT/EP 99/06882

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	ACQUIER, R.; ET AL.: "Approche du comportement des hydroxypropylcelluloses en presence d'eau, en fonction de la masse moleculaire et de la concentration" PHARMACEUTICA ACTA HELVETIAE, Bd. 67, Nr. 11, 1992, Seiten 315-320, XP000863695 Bern, CH das ganze Dokument	1-12

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internales Aktenzeichen
PCT/EP 99/06882

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP 205282 A	17-12-1986	AT	127687 T	15-09-1995
		AU	595801 B	12-04-1990
		AU	5828486 A	18-12-1986
		CA	1277913 A	18-12-1990
		DE	3650390 D	19-10-1995
		DE	3650390 T	04-04-1996
		DK	273086 A	12-12-1986
		ES	555899 A	16-07-1987
		FI	862479 A,B,	12-12-1986
		IL	78991 A	26-07-1990
		JP	2513999 B	10-07-1996
		JP	61286321 A	16-12-1986
		KR	8902949 B	14-08-1989
		NO	862287 A,B,	12-12-1986
		PT	82746 A,B	01-07-1986
		US	4940587 A	10-07-1990

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WO 01/42242 A1

(51) International Patent Classification[7]: C07D 413/10, 471/04, 487/04, 498/04, A61K 31/422, 31/437, 31/4985, 31/519, 31/424, A61P 31/04 // (C07D 471/04, 209:00, 487:04, 209:00

(21) International Application Number: PCT/US00/21093

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(25) Filing Language: English

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(30) Priority Data:
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(71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US).

(72) Inventors: PAGET, Steven; 2 Camdon Road, Belle Mead, NJ 08502 (US). HLASTA, Dennis; 5008 Davis Drive, Doylestown, NJ 18901 (US).

(74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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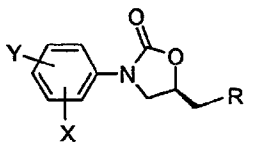
Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIBACTERIAL HETEROBICYCLIC SUBSTITUTED PHENYL OXAZOLIDINONES



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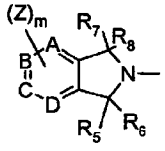

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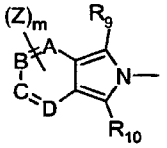


(III)

(57) Abstract: Bicyclic heterocyclic substituted phenyl oxazolidinone compounds of formula (I): wherein Y is a radical of formulae (II) or (III) in which the substituents have the meaning indicated in the description. These compounds are useful as antibacterial agents.

WO 01/42242 A1

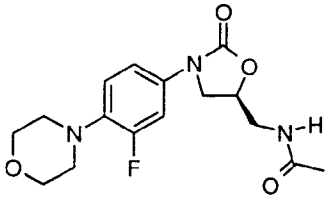
ANTIBACTERIAL HETEROBICYCLIC SUBSTITUTED PHENYL OXAZOLIDINONES

FIELD OF THE INVENTION

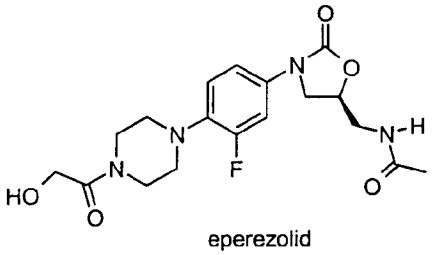
The present invention relates to the field of phenyl oxazolidinone compounds having antibacterial activity against Gram-positive and Gram-negative bacteria, pharmaceutical compositions containing the compounds, and methods of treating bacterial infections with the compounds.

BACKGROUND OF THE INVENTION

Oxazolidinones have been identified, within the last twenty years, as a new class of antibacterials which are active against numerous multidrug-resistant gram positive organisms. Particularly problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate resistant *Staphylococcus aureus* (GISA), vancomycin-resistant *enterocci* (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. As a class, oxazolidinones exhibit a unique mechanism of action. Studies have shown that these compounds selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis. Exemplary members of oxazolidinones are linezolid (see WO 95/07271) and eperezolid.



linezolid



eperezolid

U.S. Pat. No. 5,792,765 to Riedl et al. discloses a series of substituted oxazolidinones (cyanoguanidine, cyanoamidines, and amidines) useful as antibacterial medicaments.

U. S. Patent No. 5,910,504 to Hutchinson discloses a series of hetero-aromatic ring substituted phenyl oxazolidinones, including indolyl substituted compounds useful as antibacterial agents.

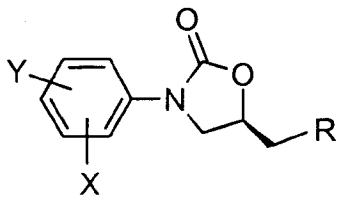
WO 98/54161 (Hester et al.) discloses amides, thioamides, ureas, and thioureas which are antibacterial agents.

WO 95/07271 (Barbachyn et al.) discloses oxazine and thiazine oxazolidinone derivatives such as linezolid and its analogs which are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiple-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*

WO 93/09103 (Barbachyn et al.) discloses substituted aryl- and heteroarylphenyloxazolidinones which are useful as antibacterial agents.

SUMMARY OF THE INVENTION

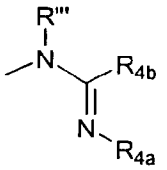
The invention provides phenyl oxazolidinone compounds of Formula I:



Formula I

wherein:

R is selected from the group consisting of OH, N_3, OR', O-Aryl, O-Heteroaryl OSO_2R'', -NR'''R'''', or



wherein:

(i) R' is straight-chain or branched acyl having up to 6 carbon atoms or benzyl;

(ii) R'' is straight-chain or branched alkyl, having up to 5 carbon atoms, phenyl or tolyl; and

(iii) R''' and R'''' are independently selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, phenyl or tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by cyano or alkoxycarbonyl having up to 4 carbon atoms, $-CO_2-R_1$, $-CO-R_1$, $-CO-SR_1$, $-CS-R_1$, $P(O)(OR_2)(OR_3)$, and $-SO_2-R_4$, in which

R_1 is selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, trifluoromethyl or phenyl, benzyl, or acyl each having up to 5 carbon atoms, straight-chain or branched alkyl having up to 6 carbon atoms, said alkyl optionally substituted by straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms, OH, cyano, up to 3 halogen atoms, and $-NR_5\ R_6$ in which R_5 and R_6 are identical or different and are selected from H, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms;

R_2 and R_3 are identical or different and are selected from hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms; and

R_4 is selected from straight-chain or branched alkyl having up to 4 carbon atoms or phenyl and;

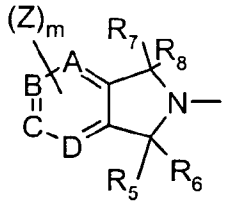
R_{4a} is CN, COR_{4c}, $COOR_{4c}$, $CONHR_{4c}$, $CO\text{-}NR_{4c}\ R_{4d}$, SO_2R_{4c}, SO_2NHR_{4c}, $SO_2\text{-}NR_{4c}\ R_{4d}$, or NO_2;

R_{4b} is H, alkyl, OR_{4c}, SR_{4c}, amino, NHR_{4c}, $NR_{4c}R_{4d}$, C1-C8-alkylaryl or mono-, di-, tri-, and per-halo C1-C8-alkyl;

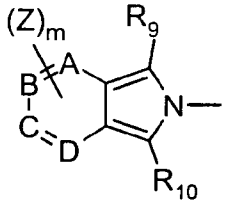
R_{4c} and R_{4d} are independently selected from H, alkyl, aryl, or in the case of any $NR_{4c}R_{4d}$ group R_{4c} and R_{4d} taken together with the nitrogen atom to which they are attached form a unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl group;

X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-$C_{1\text{-}8}$-alkyl, $C_{1\text{-}8}$ alkoxy, thio-$C_{1\text{-}8}$-alkyl, $C_{1\text{-}8}$ alkyl-amino, di($C_{1\text{-}8}$-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, $C_{1\text{-}8}$ alkyl-CO-O-, $C_{1\text{-}8}$ alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, amine, $C_{3\text{-}6}$ cycloalkyl, $C_{1\text{-}8}$ alkyl optionally substituted with one or more members selected from the group consisting of F, Cl, OH, $C_{1\text{-}8}$ alkoxyl and $C_{1\text{-}8}$ acyloxy; and

Y is a radical of Formulae II or III:



Formula II



Formula III

wherein

R_5, R_6, R_7, and R_8 are each independently H, alkyl, CN, nitro, $C_{1\text{-}8}$ alkyl, halo-$C_{1\text{-}8}$-alkyl, formyl, carboxy, alkoxycarbonyl, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, or R_5 and R_6 and/or R_7 and R_8 together form an oxo group;

R_9, and R_{10} are each independently H, halogen, alkyl, OH, CN, mercapto, nitro, C_{1-8} alkyl, halo-C_{1-8}-alkyl, C_{1-8} alkoxy, thio-C_{1-8}-alkyl, amino, C_{1-8}-alkyl-amino, di(C_{1-8}-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8}-alkyl-CO-O-, C_{1-8}-alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, or amine;

A, B, C, and D are selected from C, S, O, and N to form any five to ten membered aromatic or heteroaromatic ring, said heteroaromatic ring having one to four members selected from the group consisting of S, O, and N;

Z is selected from halogen, alkyl, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, CHO, COalkyl, amine, (dialkylamino)alkyl, said dialkylamino consisting of straight-chain or branched alkyl having up to 6 carbon atoms or phenyl or constituting a ring of 2 to 5 carbons having 0 to 2 atoms selected from S, O and N or alkoxy, or NHCO-(C_1-C_8-alkyl); and

m is 0 or 1,

and the pharmaceutically acceptable salts and esters thereof.

Compounds of the above formula are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

The present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound of Formula I.

The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a

prophylactically effective dose of the pharmaceutical composition of a compound of Formula I.

Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing specification.

DETAILED DESCRIPTION

Relative to the above description of the phenyl oxazolidinone compounds of the present invention, the following definitions apply.

Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl" may be straight or branched groups with 1-8 carbon atoms.

"Acyl" means an organic radical having the designated number of carbon atoms, derived from an organic acid by the removal of a hydroxyl group having the formula RCO, as in the case of acetyl where R is CH_3.

"Aryl" is an unsubstituted carbocyclic aromatic group including, but not limited to, phenyl, 1- or 2-naphthyl and the like. "Heteroaryl" refers to a cyclic aromatic radical having from five to ten atoms in the ring; where one to three ring atoms are independent heteroatoms such as S, O, and N, and the remaining ring atoms are carbon, for example, a pyridinyl, pyrazinyl, pyrimidinyl, pyrroyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, thienyl, furanyl, quinolinyl, or isoquinolinyl, radical and the like.

"Substituted aryl" or "substituted heteroaryl" refers to an aryl or heteroaryl substituted by independent replacement of 1-3 of the hydrogen atoms thereon with halogen, OH, CN, mercapto, nitro, C_{1-8}-alkyl, halo-C_{1-8}-alkyl, C_{1-8}-alkoxy, thio-C_{1-8}-alkyl, amino, C_{1-8}-alkyl-amine, di(C_1-C_8-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8}-alkyl-CO-O-, C_{1-8}-alkyl-CO-NH-, or carboxamide. Further, substituted-heteroaryl may be substituted with a

mono-oxo to give, for example, a 4-oxo-1-H-quinoline. Substituted-heteroaryl may also be substituted with a substituted-aryl or a second substituted-heteroaryl to give, for example, a 4-phenyl-imidazol-1-yl or a 3-pyridinyl-imidazol-1-yl, and the like.

The term "halo" or "halogen" means fluoro, chloro, bromo and iodo. (mono-, di-, tri-, and per-) halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen. P denotes phosphorus.

The compounds of the instant invention are asymmetric in the oxazolidinone ring at the 5- position and thus exist as optical antipodes. As such, all possible optical antipodes, enantiomers or diastereomers resulting from additional asymmetric centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography on a Pirkle column.

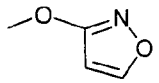
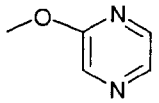
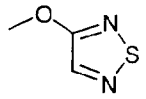
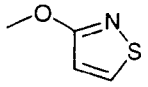
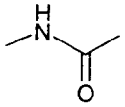
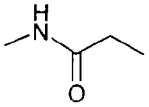
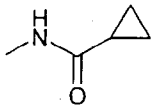
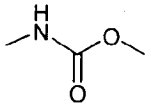
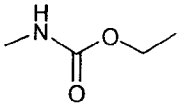
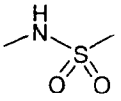
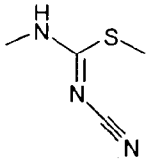
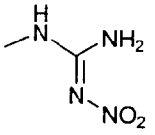
The phrase "pharmaceutically acceptable salts" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicyclic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $Ca(OH)_2$, $Al(OH)_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

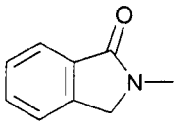
The term "subject" includes, without limitation, any animal or artificially modified animal. In the preferred embodiment, the subject is a human.

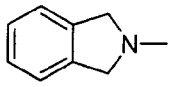
The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in presence of a currently available antimicrobial agent at its routine, effective concentration.

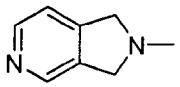
The compounds of the present invention possess antibacterial activity against Gram-positive and certain Gram-negative bacteria. They are useful as antibacterial agents for the treatment of bacterial infections in humans and animals. Particularly, these compounds have antimicrobial activity against *S. aureus*, *S. epidermidis*, *S. pneumoniae, E. faecalis*, *E. faecium*, *Moraxella catarrhalis*, and *H. influenzae*. More particularly, these compounds are useful against resistant bacteria such as MRSA and GISA, and have a low susceptibility to acquired resistance mechanisms. Compounds of Formula I which are most preferred for such purposes are those in which R is any of the following:

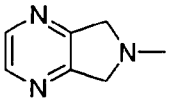













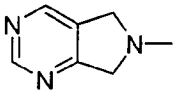
In addition Compounds of Formula I which are most preferred for such purposes are those in which Y is any of the following:

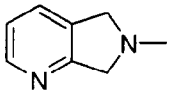
 isoindolone-;

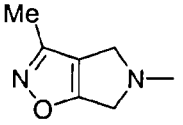

(1,3-dihydro-2H-isoindol-2-yl)-

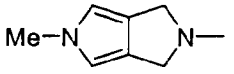

(1,3-dihydro-2H-pyrrolo[3,4-*c*]pyridin-2-yl)-

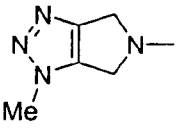

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyrazin-6-yl)-

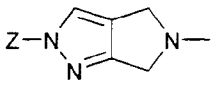

(5,7-dihydro-6H-pyrrolo[3,4-*d*]pyrimidin-6-yl)-

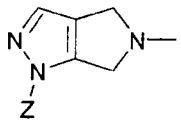

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)-


(4,6-dihydro-3-methyl-5H-pyrrolo[3,4-*d*]isoxazol-5-yl)-


(3,5-dihydro-5-methylpyrrolo[3,4-c]pyrrol-2(1H)-yl)-


(4,6-dihydro-1-methylpyrrolo[3,4-d]-1,2,3-triazol-5(1H)-yl)-





Particular examples of the present invention include the following compounds:

N-[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

N-[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

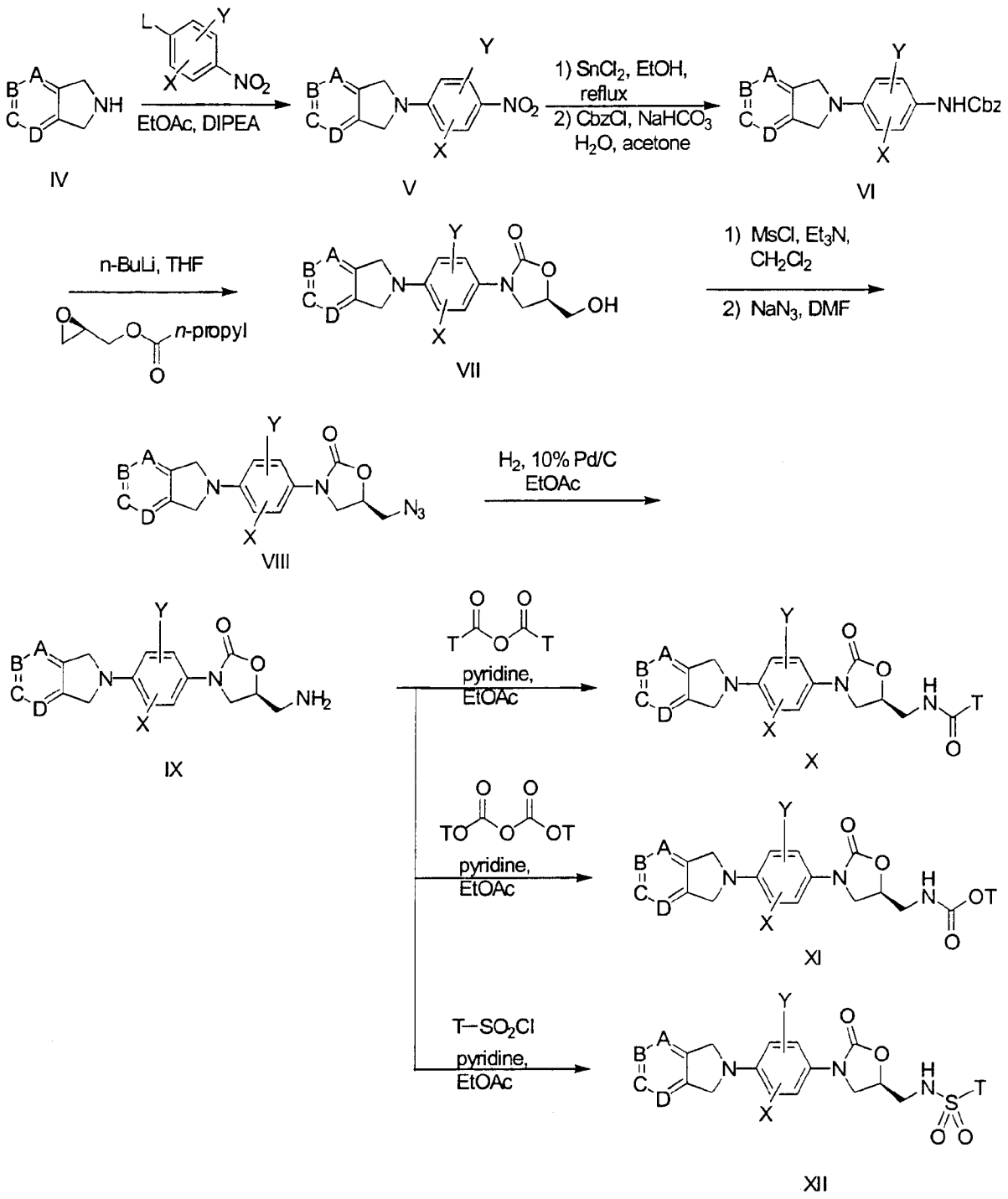
N-[[(5*S*)-3-[3-Fluoro-4-(5-oxido-2*H*-pyrrolo[3,4-*c*]pyridin-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

N-[[(5*S*)-3-[4-(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

N-[[(5*S*)-3-[4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

(5*R*)-3-[4-(5,7-Dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-3-fluorophenyl]-5-(hydroxymethyl)-2-oxazolidinone.

The compounds of Formula I that are the subject of this invention may be prepared from readily available starting materials such as isoindole (Gawley et al., *J. Org. Chem.*, 1988, *53*:5381), 6,7-dihydro-5H-pyrrolo[3,4-*c*]pyridine and 6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridine (US Pat. No. 5,371,090 to Petersen et al.) in accordance with synthetic methods well known in the art. Representative proceduresare outlined in Scheme I-V:



Scheme I

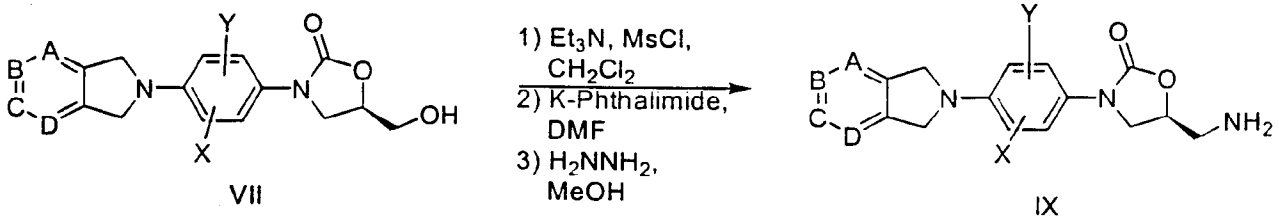
In accordance with Scheme I, bicyclic heterocycles of general formula IV are treated with a substituted nitrobenzene derivative (L is an appropriate leaving group such as a halogen of trifluoromethanesulfonyloxy) in a suitable base

and solvent, such as diisopropylamine and ethyl acetate, to give the substituted nitrophenyl compound V.

The nitrobenzene derivative V is then reduced to the aniline by an appropriate reaction, for instance by treatment with $SnCl_2$ or by catalytic hydrogenation in the presence of a suitable catalyst, such as palladium on carbon. The aniline is then treated with benzyl or methyl chloroformate and sodium bicarbonate to form the corresponding benzyl or methyl carbamate derivative VI.

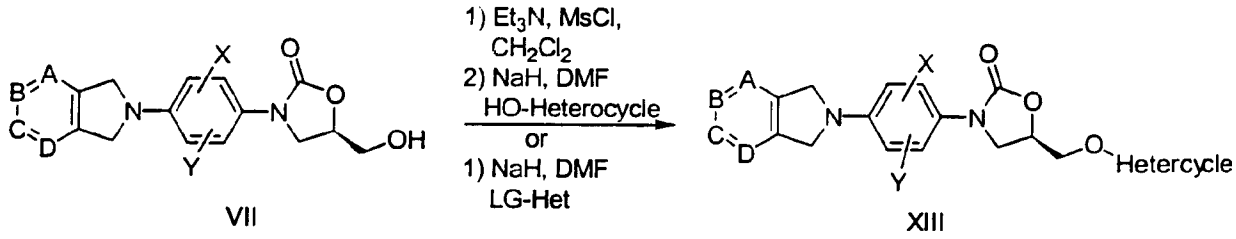
The Cbz aniline VI is then deprotonated with a lithium base such as n-butyllithium and reacted with (R)– glycidyl butyrate to afford the oxazolidinone VII. The hydroxymethyl group can then be converted to an amide as shown in Scheme I by preparation of the mesylate, conversion to azide VIII, and reduction to amine IX by an appropriate procedure such as hydrogenation. Alternatively displacement of a mesylate (Scheme II) or appropiate leaving group such as tosylate or chlorine with potassium phthalimide and removal of the phthaloyl protecting group by hydrazinolysis would provide amine IX. The amine IX can be converted to amide X by an acylation reaction using techniques known in the art, such as treatment with acetic anhydride in the presence of a base such as pyridine. Alternatively, amine IX can be converted to a carbamate XI by treatment with methylchloroformate and pyridine, or reacted with a sulfonyl chloride in an inert solvent in the presence of an organic base like pyridine to form a sulfonamide XII

Scheme II



VII IX

Scheme III

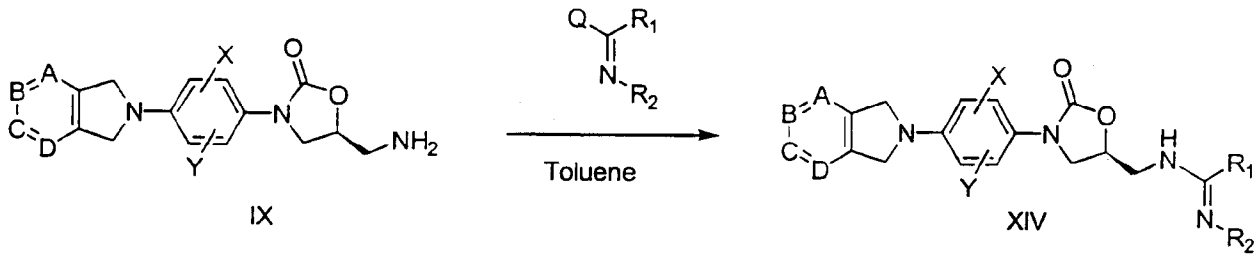


VII XIII

For the formation of oxazolidione in which R = O-Heteroaryl (XIII), the oxazolidinone carbinol VII can be converted to the corresponding mesylate or other appropriate leaving group and reacted with HO-Het (a suitible hydroxyl containing heterocycle), either in the presence of base or with HO-Het as a preformed alkoxide, in an appropriate solvent, for example DMF or acetonitrile (Scheme III). Alternatively, Mitsunobu conditions can be used to couple VII with HO-Heterocycle by treating with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in an appropriate solvent, such as THF, at a suitable temperature, preferably room temperature. Reaction conditions and leading references can be found in Gravestock et al, WO99/64416.

Furthermore, by treating VII with a suitable, non-nucleophilic base, for example NaH, the displacement of a leaving group (LG), such as chlorine or bromine, can be effected from an appropriately reactive aza-heterocycle (LG-Het)(Scheme III).

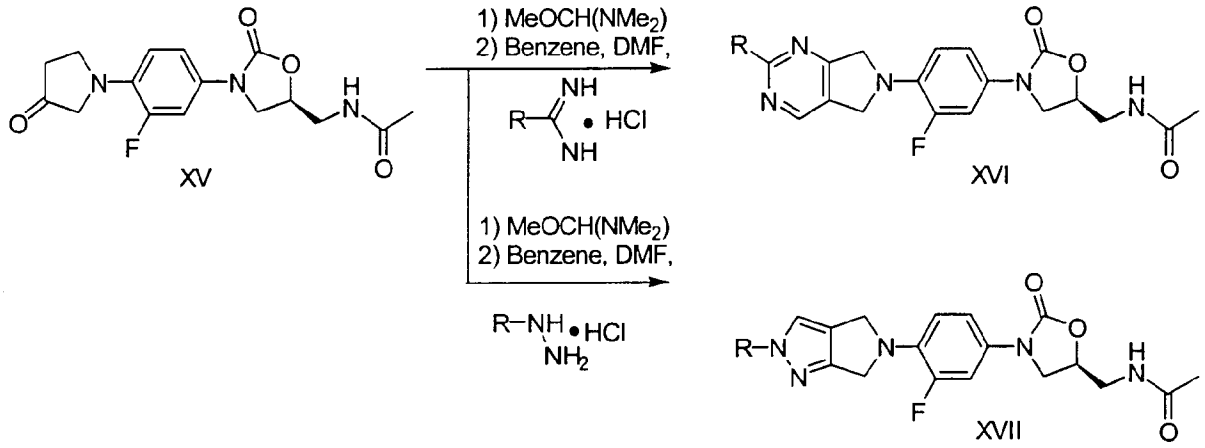
Scheme IV



IX XIV

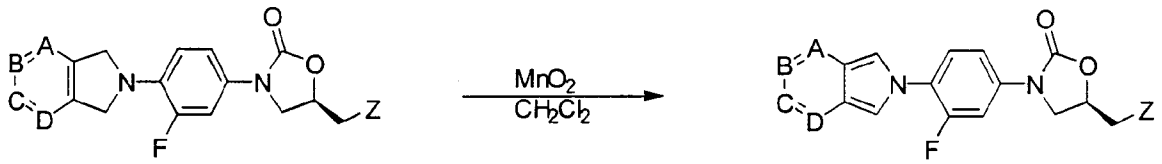
Compounds of structure XIV can be prepared as shown in Scheme IV. Amine IX can be converted to various functionalized amidines by reaction with activated imines, where Q is a leaving group such as methylthio or methoxy, in a suitable solvent, for example toluene or methanol, with or without a catalyst (such $AgNO_3$) present at a temperature range of 0-110 °C.

Scheme V



In accordance with Scheme V pyrrolidinone XV (prepared as in WO96/13502) is first reacted with methoxy-bis(dimethylamine) or other activated dimethylformamide reagent and, second, heated in a suitable solvent (for example DMF and benzene) with either substituted amidines, to form pyrrolopyrimidines oxazolidinones such as XVI, or substituted hydrazines, to form pyrrolopyrazole oxazolidinones such as XVII. Formation of the - enamine, alkoxymethylene or alkoxycarbonyl derivatives of pyrrolidinone XV, according to Brighty et al in US 5037834A, would also allow access to these systems.

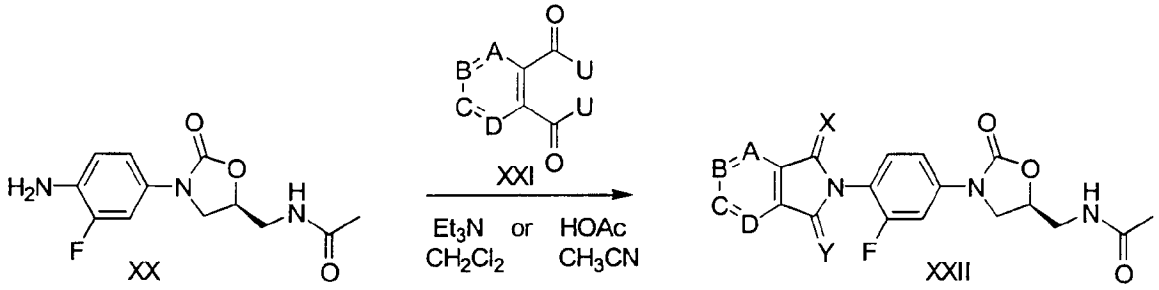
Scheme VI



XVIII XIX

As shown in Scheme VI compounds with the structure XIX can be achieved by oxidation of the various compounds, XVIII, using an appropriate oxidant (for example manganese dioxide, peroxyacetic acid, DDQ or air) in a suitable solvent such as methylene chloride.

Scheme VII



XX XXII

Oxo-derivatives of structure XXII in Scheme VII, (X = O, Y = H_2 or X = H_2, Y = O) can be constructed by reacting 1,2-aryl dicarboxaldehydes (where XXI, U = H) with aniline XX (prepared as in WO96/23788) in the presence of acids, such as acetic acid, in a suitable solvent such as methylene chloride. The di-oxo-derivatives (structure XXII where X = Y = O) are prepared from the reaction of aniline XX with selected 1,2-aryl dicarbonyl reagents with a suitable leaving group (XXI where U = Cl, Br, etc).

Definitions

All temperatures are in degrees Centigrade

Brine refers to an aqueous saturated sodium chloride solution

DMF refers to N,N-dimethylformamide

THF refers to tetrahydrofuran

Cbz refers to carbobenzyloxy

n-BuLi refers to n-butyl lithium

MS refers to mass spectrometry expressed as m/e or mass/charge unit

[M + H] refers to the positive ion of a parent plus a hydrogen atom

Ether refers to diethyl ether

rt refers to room temperature

Mp refers to melting point

CH_2Cl_2 refers to methylene chloride

NaOH refers to sodium hydroxide

MeOH refers to methanol

EtOAc refers to ethyl acetate

ppt refers to a precipitate

These compounds have antimicrobial activity against susceptible and drug resistant bacterial pathogens such as *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, Enterococcus spp., Moraxella catarrhalis* and *H. influenzae*. These compounds are particularly useful against drug resistant Gram-positive cocci such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci. These compounds are useful in the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital-acquired lung infections, bone and joint infections, and other bacterial infections.

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically--Fourth Edition", which is incorporated herein by reference.

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFU/well.

Following inoculation of the microdilution trays, the trays are incubated at 35°C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Table 1, some compounds of the present invention were tested against a variety of pathogenic bacteria resulting in a range of activities, from 1 to ≥128 μg/mL depending on the organism tested. *S. aureus* OC2878 is a MRSA and *E. faecium* OC3312 is a vancomycin resistant enterococcus.

Table 1. MIC Values of Some Compounds of Formula I

Compound No.	MIC (mg/mL) in Test Strains		
	S. aureus OC4172	*S. aureus* OC2878	*E. faecium* OC3312
1	2	2	2
2	2	1	4
3	0.5	0.25	0.5
4	1	0.5	1
5	>32	>32	>32
6	64	32	32
7	>32	8	16
8	8	4	8
9	>32	>32	>32
10	>32	8	64
11	2	1	2
12	8	2	4

13	2	1	2
14	32	16	16
15	2	2	2
16	8	8	8
17	4	2	2
18	16	16	16
19	8	4	8
20	4	2	4
21	>64	>64	>64
22	2	2	2
23	8	8	8
24	8	8	8
25	64	>128	32
26	1	0.5	1
27	8	4	8
28	0.5	0.5	0.5
29	>32	8	16
30	>128	>128	>128
31	>16	>16	>16
32	4	2	2
33	32	32	32
34	8	2	4
35	0.5	0.25	2
36	1	0.5	1
37	1	1	0.5
38	2	2	1
39	1	2	1
40	1	1	1
41	2	2	2
42	2	2	2
43	1	1	1
44	1	1	1

45	4	4	4
46	4	4	8
47	32	16	32
48	8	8	8
49	16	4	8

This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in a subject having conditions caused by or contributed to by bacterial infection, which comprises administering to the animals a compound of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention. The terms of "treating" and "treatment" include administering, either simultaneously, separately or sequentially, a pharmaceutically effective amount of a composition containing one or more of the compounds disclosed herein to a subject that desires inhibition of bacterial growth. The pharmaceutically effective amount of the compound used to practice the present invention for treatment varies depending on the manner of administration, the age, weight, and general health of the subject treated, and ultimately will be decided by physicians or veterinarians.

The compounds of the present invention may be administered to a subject such as a human by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route may vary with, for example, the condition of the recipient as well as the ease of preparation and administration.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms

as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene

glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

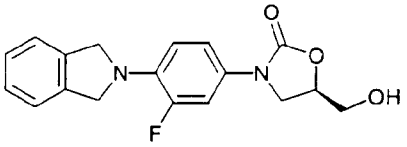
The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredients(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

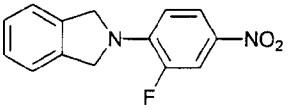
Example 1

(5*R*)-3-[4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-5-(hydroxymethyl)-2-oxazolidinone



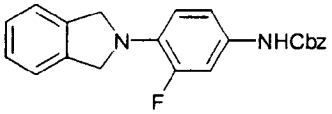
Isoindoline was synthesized employing the method of R. E. Gawley, S. R. Chemburkar, A. L. Smith, T. V. Anklekar *J. Org. Chem.* 1988, *53*, 5381.

Step 1:



To 3,4-difluoronitrobenzene (3.02 mL, 27.3 mmols) in ethyl acetate at rt was added diisopropylethylamine (5.03 mL, 28.9 mmols) and then isoindoline (3.50 g, 29.4 mmols) and stirred overnight. A yellow precipitate (ppt) formed and was collected on a filter, washed with water and ether and dried in a vacuum oven (30°C) to provide the product as a bright yellow solid (6.69 g, 95% yield). Mp = 200-202°C. MS (M + 1) = 327 m/z.

Step 2:



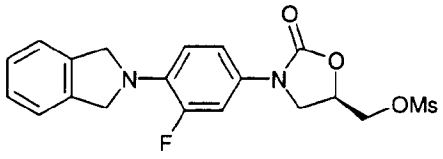
To the above nitro compound (2.62 g, 10.2 mmols) in ethanol (100 mL) was added $SnCl_2$ (9.84 g, 50.9mmols) and was refluxed for 16hrs. After cooling to rt the reaction mixture was added to 10% aq. NaOH (300 mL) and extracted with CH_2Cl_2 (6x50 mL). The combined organic washings were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give 2.63 g of an olive green solid (aniline), which was used without further purification. To this aniline in acetone (150 mL) and water (20 mL) was added $NaHCO_3$ (1.84 g, 21.9 mmols) and then benzylchloroformate (1.68 mL, 11.8 mmols). After stirring overnight the mixture was poured into ice water (100 mL) and the resulting tan precipitate was collected on a filter, washed with water and dried in a vacuum to give the Cbz aniline as a tan solid (3.50 g, 95% yield). Mp = 146-148 °C. MS (M + 1) = 363 m/z.

Step 3:

To the above Cbz aniline (0.74 g, 2.04 mmols) in THF (10 mL) at –78 °C was added *n*-BuLi (2.5 M, 0.82 mL, 2.05 mmols) dropwise. After stirring for 40 min, (R)-glycidyl butyrate (0.31 mL, 2.10 mmols) in THF (0.5 mL) was added dropwise and the resulting mixture was allowed to warm to RT overnight. A white precipitate had formed and was collected on a filter and washed with water and ether. Chromatography on silica gel with 25% ethyl acetate/hexane as eluent provided the product as a white solid (0.58 g, 87% yield). MS (M + 1) = 329 m/z.

Example 2

(5*R*)-3-[4-(1,3-Dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-5-[[(methylsulfonyl)oxy]methyl]-2-oxazolidinone

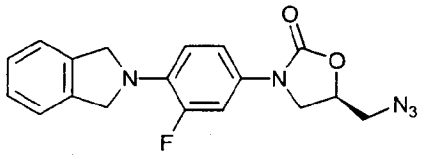


To the oxazolidinone carbinol from Example 1 (0.58 g, 1.78 mmols), in DMF (10 mL) and acetonitrile (10 mL) at 0 °C was added triethylamine (0.74 mL, 5.31 mmols) and, after 10 min, methanesulfonyl chloride (0.28 mL, 3.62 mmols). After allowing the reaction mixture to warm to RT over an hour

starting material was still present so cooling and addition of triethyl amine (0.37 mL, 2.65 mmols) and methanesulfonyl chloride (0.14 mL, 1.81 mmols) was repeated. The mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (6 X 20 mL), washed with brine (4 x 10mL), dried over Na_2SO_4, concentrated to afford the crude product as a brown oil (0.95 g). MS (M + 1) = 407 m/z.

Example 3

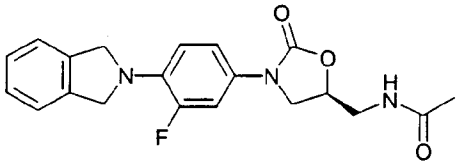
(5*R*)-5-(Azidomethyl)-3-[4-(1,3-dihydro-1-oxo-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxazolidinone



To the mesylate from Example 2 (0.95 g, 1.78 mmols) in DMF (25 mL) was added sodium azide (0.47 g, 7.23 mmols) and heated to 70°C for 16 hrs. After cooling to rt water was added and the mixture extracted with ethyl acetate (6X25 mL), washed with brine (4x10 mL), dried over Na_2SO_4, concentrated to give 0.48 g of a tan solid. MS (M + 1) = 354 m/z.

Example 4

N-[[(5*S*)-3-[4-(1,3-Dihydro-2*H*-isoindol-2-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

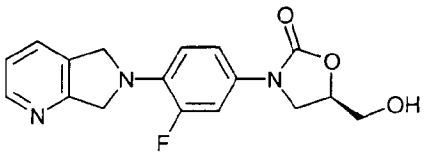


Compound 1

The azide from Example 3 in ethyl acetate (25 mL) was placed in a Paar flask and nitrogen bubbled through for 15 min whereupon 10% Pd/C (0.15 g, 0.14 mmol) was added. The mixture was pressurized with 50 psi of H_2 (*g*) and shaken for 16 hrs whereupon an additional amount of 10% Pd/C (0.15 g, 1.4 mmols) was added and the mixture shaken for an additional 6 hrs (at this

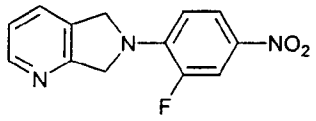
point MS (M + 1) = 328 m/z). After placing the mixture under nitrogen, pyridine (0.22 mL, 2.72 mmol) and then Ac_2O (0.51 mL, 5.30 mmol) were added and the mixture stirred for 2 hrs. The mixture was filtered through celite, washing with ethyl acetate (100 mL), concentrated, and chromatographed on silica (gradient elution 1%-5% $MeOH/CH_2Cl_2$) and then triturated with ethyl acetate (3X3 mL) to give 0.19 g of a white solid (Compound 1, 29% yield for 4 steps). Mp = 240-242°C. MS (M + 1) = 370 m/z.

Example 5



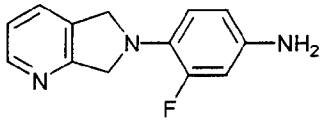
Compound 2

Step 1:



6,7-Dihydro-6-(2-fluoro-4-nitrophenyl)-5H-pyrrolo[3,4-b]pyridine: To 6,7-dihydro-5H-pyrrolo[3,4-b]pyridine dihydrochloride salt (as described by Petersen, et al. (Bayer) EP0520277A2)(42.8 g, 222 mmols) in DMF (1.2 L) was added 2,4-difluoronitrobenzene (25 mL, 224 mmols). The mixture was heated to 60°C and DIPEA (195 mL, 1.12 mols) was added dropwise from an addition funnel over 2 hrs. After heating overnight the reaction mixture was cooled to rt, poured into water (3 L), filtered and dried in a vacuum oven (50°C) to provide a yellow-green solid (53.8 g, 94% yield). MS (M + 1) = 260 m/z.

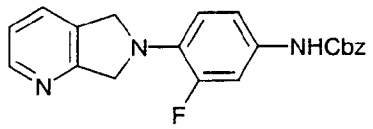
Step 2:



6,7-Dihydro-6-(2-fluoro-4-aminophenyl)-5H-pyrrolo[3,4-b]pyridine

To the above nitro compound (53.8 g, 208 mmol) in THF (175 mL) and methanol (600 mL) was added ammonium formate (59.0 g, 907 mmol). Nitrogen was bubbled through the reaction for approximately 30 minutes whereupon 10% Pd/C (2.20 g, 21 mmols) was added. After stirring overnight at rt under an atmosphere of nitrogen the reaction mixture was filtered through a pad of Celite, washing thoroughly with methanol (400 mL), and concentrated to a volume of ca. 200 mL. Water (300 mL) was added and the mixture extracted with ethyl acetate (5X200 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and utilized directly in the next step without further purification. MS (M + 1) = 230 m/z.

Step 3:



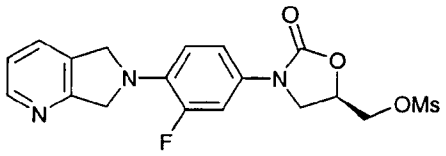
6,7-Dihydor-6-(2-fluoro-4-(Aminocarboxybenzyl)phenyl)-5H-pyrrolo[3,4-b]pyridine The above aniline (~208 mmols) in acetone (1 L) and water (160 mL) was cooled to 0°C whereupon sodium bicarbonate (37.4 g, 445 mmols) was added followed by the dropwise addition of benzylchloroformate (34.2 mL, 228 mmols). The reaction mixture was allowed to warm to room temperature and stirred overnight whereupon a ppt formed. The reaction was poured into ice water (2 L) and the resulting precipitate was collected by filtration. The solid was washed with water and dried in a vacuum oven (50°C) to afford the Cbz derivative (73.0 g, 97% yield) as a salmon colored powder. MS (M + 1) = 364 m/z.

Step 4:

(Compound 2). The above Cbz derivative (40.8 g, 112 mmols) in THF (1 L) was cooled to –78°C under a nitrogen atmosphere. To this mixture was added n-BuLi (2.5 M, 45.8 mL, 114.5 mmols) dropwise via syringe over fifteen minutes. The reaction was warmed to room temperature and allowed to stir

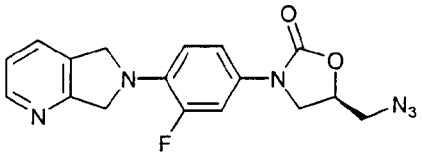
for 45 minutes before again being cooled to –78°C. At this point (R)-glycidyl butyrate (17.2 mL, 117 mmols) was added and the reaction mixture allowed to warm to rt overnight during which time a precipitate formed. The ppt was collected, washed with several portions of ether (5X100 mL) and dried in a vacuum oven (50°C) to afford 40.6 g of the ether solvate of the lithium alkoxide as a tan fluffy powder. This material was then washed with several portions of water (4X200 mL) and dried in a vacuum oven (50°C) to afford the oxazolidinone alcohol (34.1 g, 92% yield) as a tan granular solid. Mp = 208-212°C, decomp. MS (M + 1) = 330 m/z.

Example 6



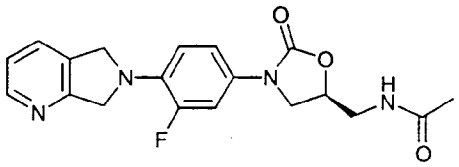
Oxazolidinone Mesylate. The above oxazolidinone carbinol (from Example 4) (33.8 g, 103 mmols) was suspended in DMF (1.25 L, previously degassed with nitrogen) at rt under a nitrogen atmosphere. Triethylamine (50 mL, 360 mmols) was added followed by the dropwise addition of methanesulfonyl chloride (13.5 mL, 174 mmols). After stirring for 3 hrs the reaction mixture was poured into water (200 mL) and methylene chloride (1 L) added. A ppt was filtered off, washed with water (3X200 mL) and dried in a vac oven (50°C) to afford the mesylate as a tan solid (28.1 g, 67%). The organic layer was dried (Na_2SO_4), filtered and evaporated to also afford the mesylate (11.7 g, 28% yield) as a tan solid. Both where characterized with MS (M + 1) = 408 m/z.

Example 7



Oxazolidinone Azide. The above mesylate (from Example 5) (27.8 g, 68.2 mmols) and sodium azide (17.7 g, 271 mmols) in anhydrous DMF (1 L), previously degassed with nitrogen, were heated 95°C for 6 hr under a nitrogen atmosphere. After cooling, the mixture was poured into stirred ice water (2 L) and formed a flocculant white ppt. The ppt was collected on a filter and washed with water (4X200 mL), dried in a vac oven (50°C) to afford the azide as a light beige solid (22.7 g, 94% yield). Mp = 175-180°C, decomp. MS (M + 1) = 355 m/z.

Example 8

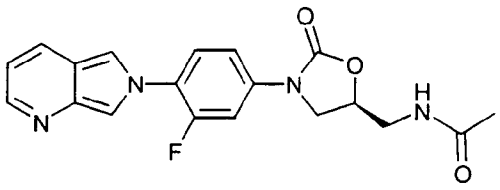


Compound 3

Oxazolidinone Acetamide. The above azide (from Example 6)(21.67 g, 61.16 mmol) dissolved in DMF (400 mL) and THF (500 mL) was degassed with nitrogen for 30 minutes whereupon 10% Pd/C (4.74 g, 4.4 mmols) was added and the reaction hydrogenated on a Parr apparatus (60 psi of hydrogen) for 14 hr. The reaction mixture was removed from the Parr apparatus and placed under a nitrogen atmosphere whereupon pyridine (5.44 mL, 67.3 mmols) and acetic anhydride (6.35 mL, 67.3 mmols) were added. After stirring for 1 hr the

reaction mixture was filtered through a pad of Celite, washing thoroughly with methanol and then copious amounts of 50% MeOH/CH_2Cl_2 (ca. 2 L). The filtrate was evaporated to afford the crude acetamide in DMF. The mixture was slowly added to water (2 L) and the ppt collected on a filter, washed with water (5X400 mL) and dried in a vac oven (50 °C) to provide the acetamide as an analytically pure white solid (14.2 g, 63% yield). The combined filtrates were extracted with methylene chloride (5X200 mL), dried over Na_2SO_4 and concentrated. Water was added to the residue and the resulting ppt was filtered off and dried in a vac oven (50 °C) to afford a second crop of the acetamide as a light tan, fluffy solid (5.61 g, 25%). For the analytically pure material Mp = 229-230 °C, decomp. MS (M + 1) = 371 m/z.

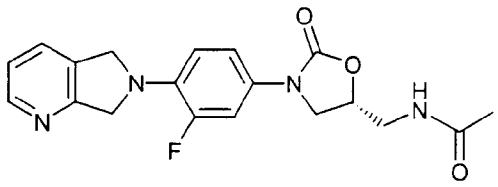
Example 9



Compound 4

The above acetamide from Example 8 (2.51 g, 6.78 mmols) was taken up in CH_2Cl_2 and MnO_2 added (23.9 g, 234 mmols). After stirring overnight the reaction mixture was filtered through celite, concentrated and chromatography on silica with 10% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.48 g, 19% yield). Mp = 220-225 °C decomp. MS (M + 1) = 369 m/z.

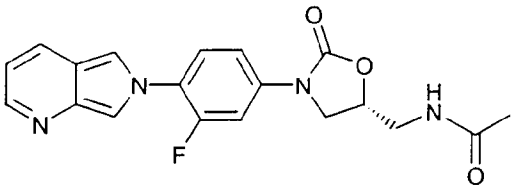
Example 10



Compound 5

Compound 5 was prepared as in Example 8 except (S)-glycidyl butyrate was employed in the oxazolidinone formation. The product was isolated as a light tan solid. Mp = 227-230°C decomp. MS (M + 1) = 371 m/z.

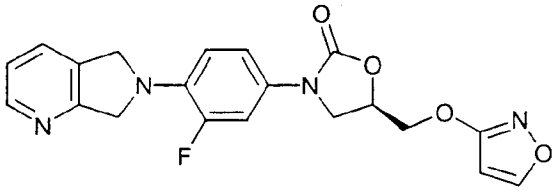
Example 11



Compound 6 oxidized enantiomer

Compound 6 was prepared as in Example 9 and isolated as a light yellow solid. Mp = 181-185°C decomp. MS (M + 1) = 369 m/z.

Example 12

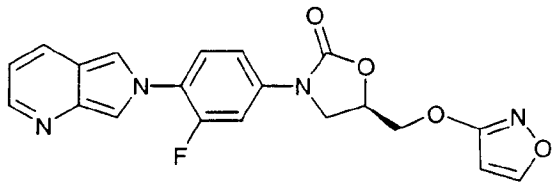


Compound 7

To 5-hydroxyisoxazole (prepared as in *Chem Pharm Bull* **1966**, *14*(11), 1277) (0.174 g, 2.04 mmols) in DMF was added NaH (60% in oil)(0.105 g, 2.62 mmols). After stirring for 30 min the mesylate (from Example 6) (0.744g, 1.82

mmols) was added in one portion and the mixture stirred at 60°C overnight. After cooling to rt water was added and a ppt was collected on a filter, air dried and chromatographed on silica with 2.5% MeOH/CH_2Cl_2 as eluent to afford the product as a white solid (0.140 g, 19 % yield). Mp = 182-185°C. MS (M + 1) = 397 m/z.

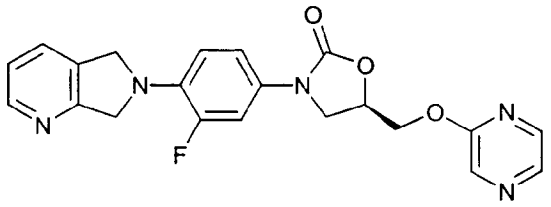
Example 13



Compound 8

To the above oxazolidinone (from Example 12) (0.264 g, 6.66 mmols) was taken up in CH_2Cl_2 and MnO_2 added (1.66 g, 16.2 mmols) in two portions over two days. After stirring for two days the reaction mixture was filtered through celite, concentrated and chromatographed on silica with 10% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.086 g, 32% yield). Mp = 133-135°C. MS (M + 1) = 395 m/z.

Example 14



Compound 9

To NaH (60% by wt in oil)(0.03 g, 0.76 mmol) in DMF (5 mL) was added oxazolidinone carbinol (from Example 5) (0.23 g, 0.71 mmol) in four portions. After stirring for 30 min 2-chloropyrazine (0.065 mL, 0.71 mmol) was added

via syringe and stirred overnight at rt. Water was added and a ppt was collected on a filter, air dried and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a white solid (0.067 g, 23 % yield). Mp = 225-230°C. MS (M + 1) = 408 m/z.

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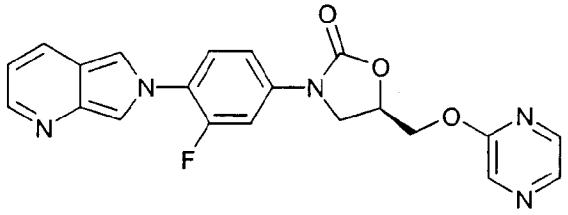
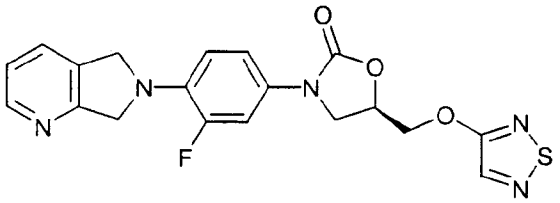
Example 15



Compound 10

The above oxazolidinone (from Example 14) (0.024 g, 0.058 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (0.07 g, 0.7 mmol). After stirring overnight the reaction mixture was filtered through Celite and concentrated to afford the product as a very light yellow solid (0.015 g, 64% yield). Mp = 192-194°C. MS (M + 1) = 406 m/z.

Example 16

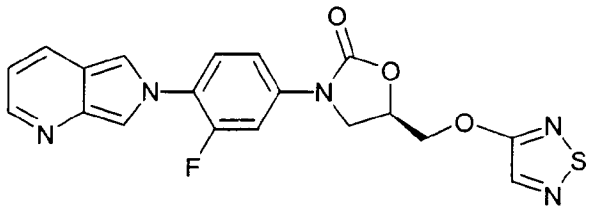


Compound 11

To a suspension of the oxazolidinone carbinol (prepared in Example 5) (330 mg, 1.0 mmol), triphenylphosphine (260 mg, 1.1 mmols) and 4-hydroxy-1, 2, 5-thiadiazole (100 mg, 1.0 mmol) (as prepared in U.S Patent 3,391,150 [7/2/68]) in THF (8 mL) was added diisopropylazodicarboxylate (0.20 mL, 1.1 mmols). After stirring overnight at rt the reaction mixture was filtered, washed

with methanol, and air dried to afford a yellow crystalline solid (60 mg, 15% yield). Mp = 185-187°C. MS (M + 1) = 414 m/z.

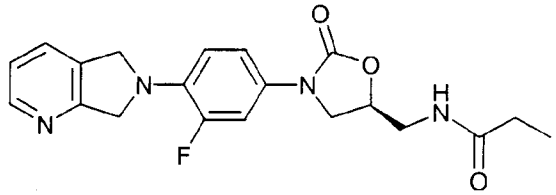
Example 17



Compound 12

To the oxazolidinone (prepared in Example 16) (160 mg, 0.39 mmol) suspended in CH_2Cl_2 (1.0 mL) was added MnO_2 (four additions of 150 mg over four days). The reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (15 mL), and concentrated under reduced pressure to afford the product as a white crystalline solid (63 mg, 40% yield). Mp = 185-188°C. MS (M + 1) = 412 m/z.

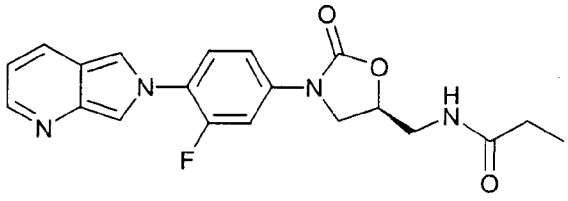
Example 18



Compound 13

To the amine (as prepared in Example 8) (100 mg, 0.30 mmol) and potassium carbonate (100 mg, 0.72 mmol) suspended in methanol (1.0 mL), was added propionyl chloride (50 mg, 0.54 mmol). After stirring overnight at 80°C the reaction mixture was cooled and water was added. A precipitate was filtered off, washed with methanol and air dried to afford the product as a brown crystalline solid (15 mg, 13 % yield). Mp = 110-112°C. MS (M + 1) = 385 m/z.

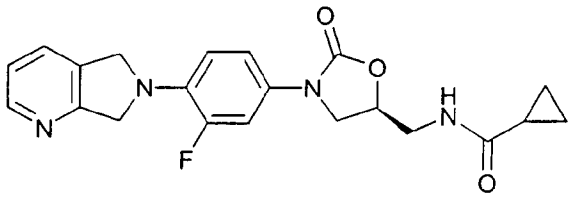
Example 19



Compound 14

To the amide (prepared in Example 18) (15 mg, 0.04 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (200 mg) at rt. After stirring overnight, the reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as an light brown crystalline solid (1.6 mg, 8 % yield). MS (M + 1) = 383 m/z.

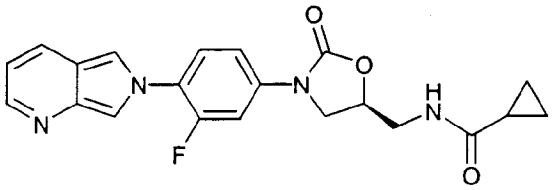
Example 20



Compound 15

To the amine (as prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL), was added cyclopropyl carbonyl chloride (120 mg, 1.15 mmols). After stirring at rt overnight, the reaction mixture was filtered, rinsed with methanol, and then concentrated to dryness under reduced pressure. The resulting solid residue was triturated with water and filtered to afford the product as a brown crystalline solid (36 mg, 50 % yield). Mp = 235-240°C. MS (M + 1) = 397 m/z.

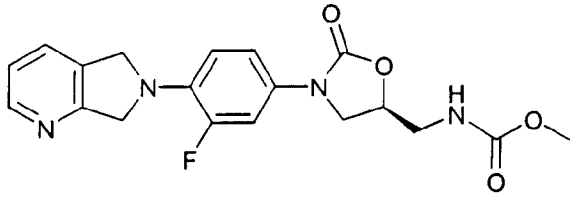
Example 21



Compound 16

To the amide (prepared in Example 20) (36 mg, 0.09 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (three portions of 100 mg over three days) at rt. The reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as an off-white crystalline solid (3 mg, 8 % yield). MS (M + 1) = 395 m/z.

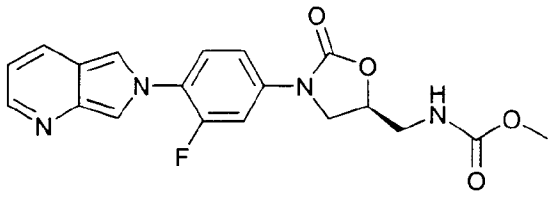
Example 22



Compound 17

To the amine (prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL), was added dropwise methyl chloroformate (120 mg, 1.27 mmols). After stirring for four hours at rt, the reaction mixture was filtered, diluted with water, and concentrated under reduced pressure to remove the methanol. The aqueous solution was extracted with ethyl acetate (5X5 mL). The combined organics were washed with water, dried over $MgSO_4$, filtered, and concentrated to provide an oil which was triturated with ether to afford a brown crystalline solid (35 mg, 50% yield). MS (M + 1) = 387 m/z.

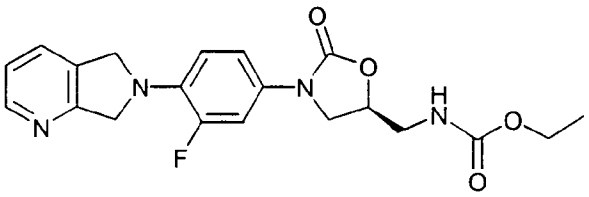
Example 23



Compound 18

To the carbamate (prepared in Example 22) (33 mg, 0.08 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (150 mg). After stirring overnight at rt the reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as a yellow crystalline solid (6.0 mg, 18% yield). MS (M + 1) = 385 m/z.

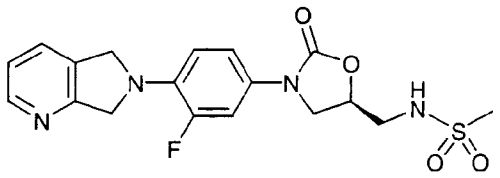
Example 24



Compound 19

To the amine (prepared in Example 8) (60 mg, 0.18 mmol) and potassium acetate (60 mg, 0.61 mmol) suspended in methanol (1.0 mL) was added dropwise ethyl chloroformate (0.1 mL, 1.04 mmols). After stirring overnight at rt the reaction mixture was filtered, diluted with water, and concentrated under reduced pressure to remove the methanol. The aqueous solution was extracted with ethyl acetate (5X5 mL). The combined organics were washed with water, dried over $MgSO_4$, filtered, and concentrated. The resulting semi-solid was treated with water, filtered and air-dried to afford a brown crystalline solid (18 mg, 30% yield). MS (M + 1) = 401 m/z.

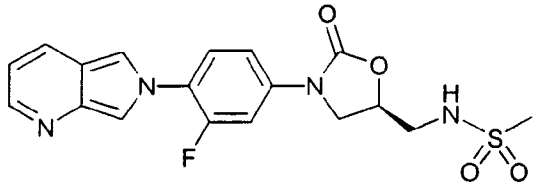
Example 25



Compound 20

To the amine (prepared in Example 8) (95 mg, 0.29 mmol) suspended in pyridine (0.5 mL) was added methane sulfonylchloride (0.08 mL, 1.0 mmol). After stirring overnight at rt the pyridine was removed under a stream of nitrogen. The residue was treated with water, filtered and air-dried to afford a brown solid (45 mg, 38% yield). Mp = 172-176 °C. MS (M + 1) = 407 m/z.

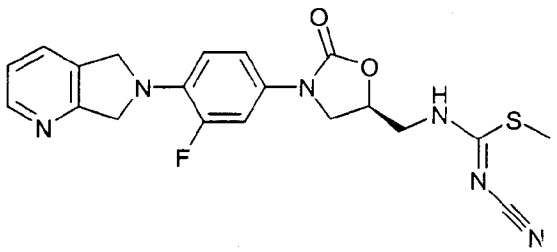
Example 26



Compound 21

To the sulfonamide (prepared in Example 25) (10 mg, 0.02 mmol) suspended in CH_2Cl_2 (1.0 mL), was added MnO_2 (100 mg, 10 mmols). After stirring overnight the reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as a brown crystalline solid (0.5 mg, 5% yield). MS (M + 1) = 405 m/z.

Example 27

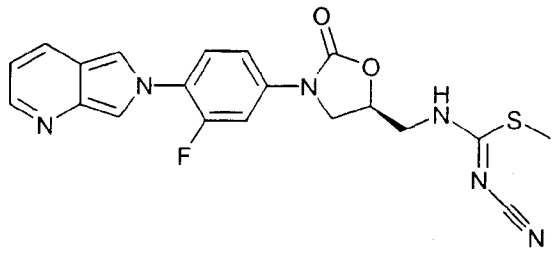


38

Compound 22

To the amine (prepared in Example 8) (200 mg, 0.61 mmol) suspended in toluene (8 mL), was added dimethyl-N-cyanodithioiminocarbonate (89 mg, 0.61 mmol). After stirring overnight at reflux the toluene was decanted and the oily residue treated with methanol, filtered, and air-dried to afford a brown crystalline solid (62 mg, 20% yield). Mp = 204-207°C. MS (M + 1) = 427 m/z.

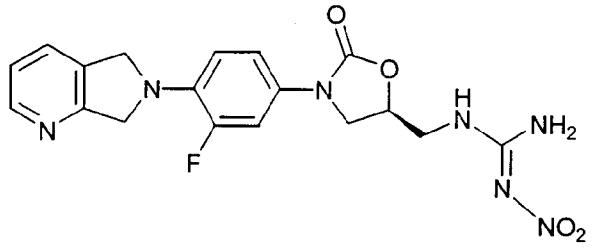
Example 28



Compound 23

A suspension of the thioimidate (from Example 27) (45 mg, 0.10 mmol) and MnO_2 (200 mg, 2.0 mmols) in CH_2Cl_2 were stirred at rt for one day whereupon a second addition of MnO_2 (150 mg, 1.5 mmols) was added. After an additional day of stirring the mixture was filtered through Celite, washed with CH_2Cl_2 (10 mL), concentrated to afford a yellow crystalline solid (20 mg, 45% yield). MS (M + 1) = 426 m/z.

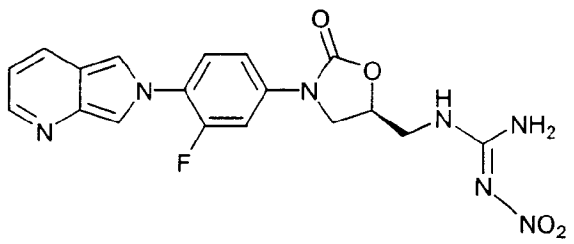
Example 29



Compound 24

A suspension of the amine (prepared in Example 8) (165 mg, 0.5 mmol) and 2-methyl-1-nitro-2-thiopseudourea (94 mg, 0.70 mmol) (as prepared as in EP 0539204/ 1993) in methanol (2 mL) was refluxed for four hours. After cooling to rt the reaction mixture was filtered and air dried to afford a yellow crystalline solid (50 mg, 24% yield). Mp = 202-206 °C. MS (M + 1) = 416 m/z.

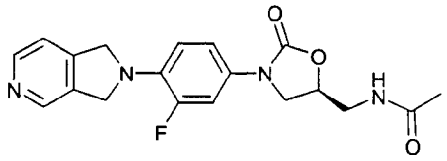
Example 30



Compound 25

To the nitroguanidine (prepared in Example 29) (35 mg, 0.08 mmol) suspended in CH_2Cl_2 (1.0 mL) was added MnO_2 (three additions of 100 mg over three days). The reaction mixture was filtered through a plug of Celite, washed with CH_2Cl_2 (10 mL), and concentrated under reduced pressure to afford the product as a yellow crystalline solid (1.6 mg, 4% yield). MS (M + 1) = 414 m/z.

Example 31

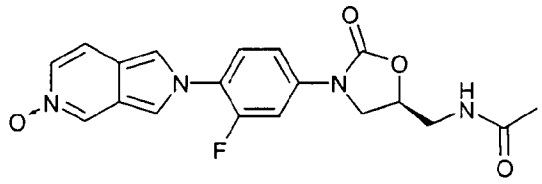


Compound 26

The starting material 6,7-dihydro-5H-pyrrolo[3,4-*c*]pyridine was prepared as in US Pat. No. 5,371,090 to Petersen et al. Compound 26 was then prepared as

in Example 8 except the acetamide was recrystallized from acetonitrile to give a light tan solid. Mp = 182-190°C decomposition. MS (M + 1) = 371 m/z.

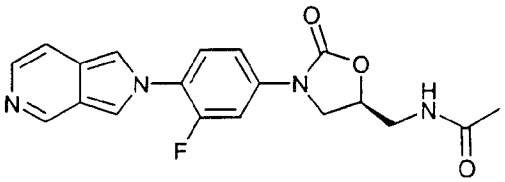
Example 32



Compound 27

Compound 27 was isolated from the final step of Example 31 via chromatography (5% MeOH/CH_2Cl_2 as eluent) of the mother liquors collected from recrystallization. Light yellow solid, Mp = 219-225°C decomp. MS (M + 1) = 385 m/z.

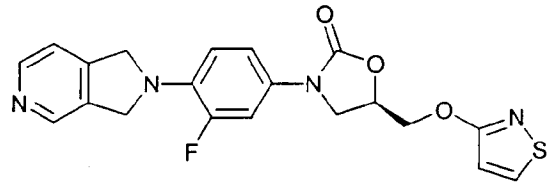
Example 33



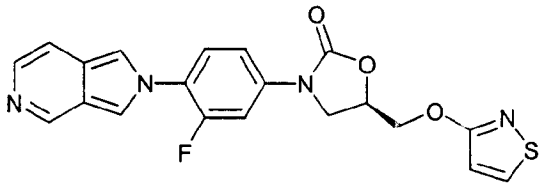
Compound 28

Compound 28 was prepared as in Example 9 except with 10% MeOH/CH_2Cl_2 as eluent. Light yellow solid, Mp = 219-225°C decomposition. MS (M + 1) = 369 m/z.

Example 34



Compound 29

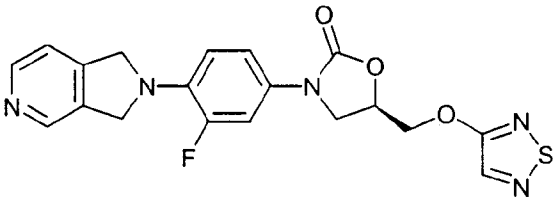


Compound 30

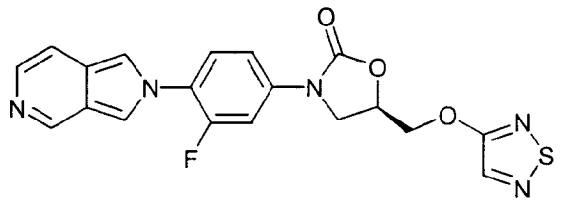
Isothiazole (0.088 g, 0.87mmol)(prepared as in *J Heterocyclic Chem* **1971**, *8*, 591) was added portionwise at rt to a suspension of sodium hydride (0.036 g, 0.91 mmol, 60% in oil) in DMF (4 mL) under nitrogen. The mixture was stirred for 30 minutes whereupon the mesylate from Example 31 (0.31 g, 0.76 mmol), in DMF (10 mL), was added all at once. After stirring for 6 hours at 60°C the reaction mixture was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3x50 mL). The combined organics were washed several times with water, then once with brine, dried over sodium sulfate, concentrated, and chromatographed on silica with 5% MeOH/EtOAc as eluent. Two products were isolated from the chromatography: 0.050g of Compound 29; and 0.022 g of Compound 30. Overall yield, 30%.

Compound 29 MS (M+1) = 413.0
Compound 30 MS (M+1) = 411.1

Example 35



Compound 31

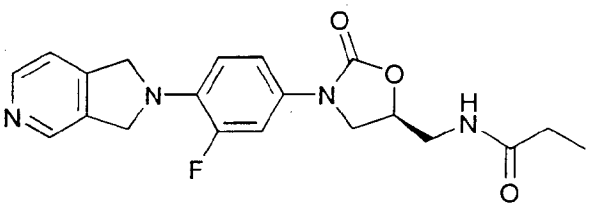


Compound 32

To a suspension of sodium hydride (0.036 g, 0.91mmol, 60% in oil) in DMF (4 mL) at rt under nitrogen was added portion wise 4-hydroxy-1, 2, 5-thiadiazole (0.088 g, 0.87 mmol) (as prepared in U.S Patent 3,391,150 [7/2/68]). After stirring for 30 min the mesylate from Example 31 (0.310 g, 0.76 mmol), in DMF (10 mL), was added all at once. After stirring for 6 hours at 60 C the reaction mixture was cooled to rt, diluted with water (50 mL), and extracted with ethyl acetate (3x50 mL). The combined organics were washed several times with water, then once with brine, dried over sodium sulfate, concentrated, and chromatographed on silica with 2% MeOH/EtOAc as eluent. Two products were isolated from the chromatography: 0.035 g of Compound 31; and 0.0093 g of Compound 32. Overall yield, 14%.

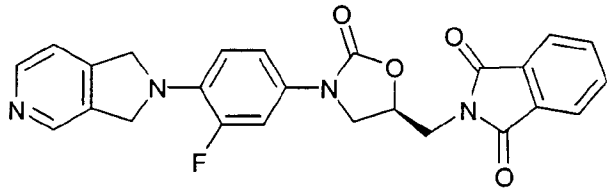
Compound 31 MS (M+1) = 414.0
Compound 32 MS (M+1) = 412.1

Example 36

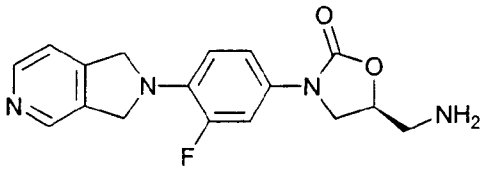


Compound 33

Step 1:



To the mesylate from Example 31 (2.45 g, 6.01 mmol) dissolved in degassed DMF (100 mL) under nitrogen was added potassium phthalimide (2.23 g, 12.0 mmols). After heating at 65°C for 3 hours the reaction mixture was cooled, poured into water (300 mL), and extracted with methylene chloride (3x200 mL). The combined organics were washed with water (3x150 mL) dried over sodium sulfate, concentrated to a tan solid. This solid was washed with water and dried in a high vacuum oven at 50°C to afford 2.20 g (80%) of the oxazolidinone phthalimide. MS= 459.1 (M+1)



Step 2:

To the above phthalimide (0.97 g, 2.1 mmols) in degassed methanol (30 mL) under nitrogen was added hydrazine monohydrate (0.2 mL, 4.3 mmols) dropwise. After refluxing for 12 hours the reaction mixture was cooled to rt, and concentrated, suspended CH_2Cl_2 and filtered. The crude oxazolidinone amine was concentrated and used without further purification.

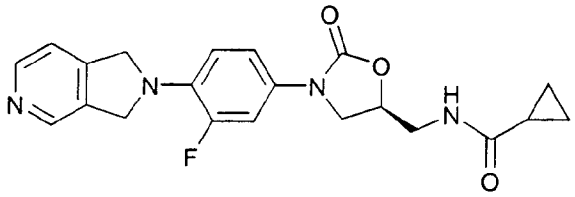
Step 3:

Compound 33,

To the crude amine (0.14 g, 0.44 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.14 mL, 18 mmols) followed by propionyl chloride (0.76 mL, 0.88 mmol).

After stirring for 5 hrs at rt the solution was poured into water (20 mL) and extracted with methylene chloride (3x10 mL). The combined extracts were washed with water (10 mL) and 1 M NaOH (aq) (10 mL), dried over sodium sulfate, concentrated and chromatographed using neat EtOAc as eluent to afford the propionyl amide as a gold oil (0.020 g, 12% yield). MS= 385.2 (M+1)

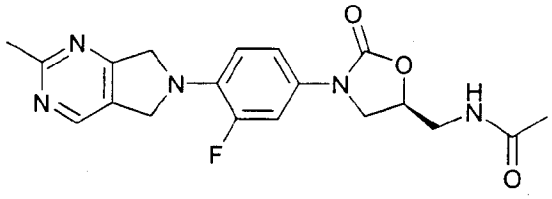
Example 37



Compound 34

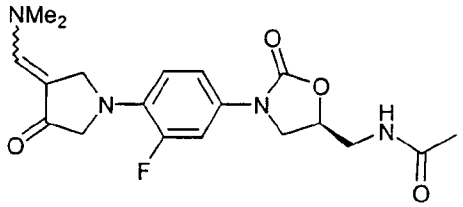
To the crude amine (as prepared in Example 36) (0.144 g, 0.437 mmol) in methylene chloride (5 mL) was added pyridine (0.14 mL, 1.7 mmols), followed by cyclopropane carbonyl chloride (0.08 mL, 0.88 mmol). After stirring for 5 hrs at rt the solution was poured into water (20 mL) and extracted with methylene chloride (3x10 mL). The combined extracts were washed with water (10 mL) and 1 M NaOH (aq) (10 mL), dried over sodium sulfate, concentrated and chromatographed using a gradient elution of 1% to 5% to 10% MeOH/ EtOAc. The desired product eluted with 5% MeOH/ EtOAc and was concentration to afford the product as a white powder (0.012 g, 7% yield). MS= 397.2 (M+1)

Example 38



Compound 35

Step 1:



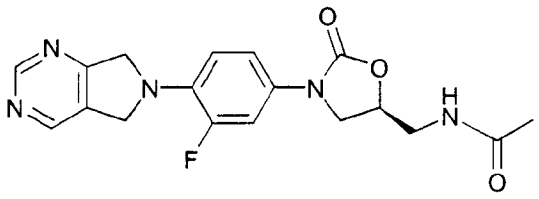
To *N*-[(3-pyrrolidinone-3-fluorophenyl) 5-oxazolidinyl]methyl acetamide (prepared according to W096/13502)(0.150 g, 0.447 mmols) was added methoxy-bis(dimethylamino)methane (1 mL). After heating at 50°C for 15 min the reaction mixture was concentrated to provide the crude β-ketoenamine which was used without further purification.

Step 2;

Compound 35

To ethanolic NaOEt (made from 0.027 g Na in 3 mL EtOH) was added acetamidine hydrochloride (0.113 g, 1.19 mmols) and the above β-ketoenamine oxazolidinone acetamide. After refluxing for 3 hrs the reaction mixture was cooled to rt, concentrated, taken up in chloroform, and washed with water (3x8 mL). After drying over sodium sulfate the crude product was concentrated, dissolved in 5% MeOH/ EtOAc, and filtered to afford the product as an off-white solid (0.052 g, 45% yield). Mp = 234°C, decomp. MS = 385.9 (M+1)

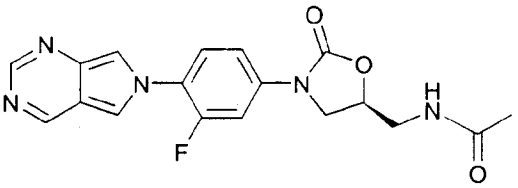
Example 39



Compound 36

To *N*-[(3-pyrrolidinone-3-fluorophenyl) 5-oxazolidinyl]methyl acetamide (prepared according to W096/13502)(0.099 g, 0.29 mmol) was added methoxy-bis(dimethylamino)methane (1.0 mL). After heating at 50°C for 2 hrs the reaction mixture was concentrated to provide the crude β-ketoenamine. To this mixture was added benzene (5 mL), DMF (1 mL) and formamidine acetate (0.55 g, 5.3 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a white powder (0.037 g, 34% yield). Mp = 230-232°C. MS (M + 1) = 372 m/z.

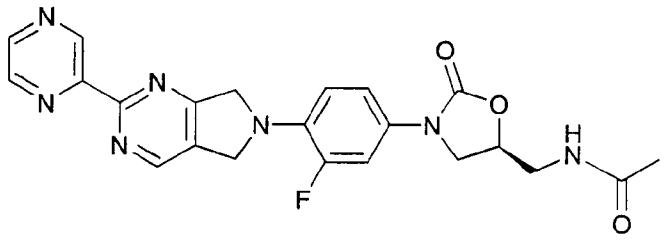
Example 40



Compound 37

The above acetamide from Example 39 (0.020 mg, 0.054 mmol) was taken up in CH_2Cl_2 (5 mL) and MnO_2 added (0.10 g, 0.98 mmol). After stirring overnight at rt the reaction mixture was filtered through Celite and concentrated to afford the product as a light yellow solid (0.016 g, 80% yield). Mp = 164-166°C. MS (M + 1) = 370 m/z.

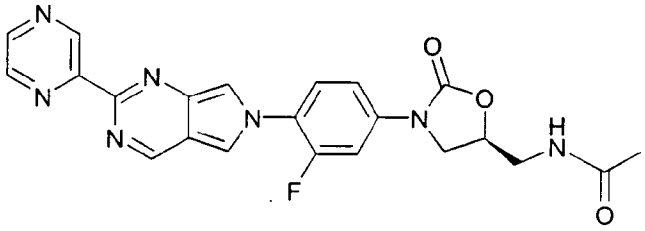
Example 41



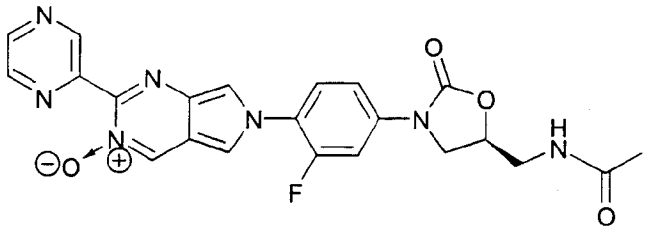
Compound 38

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and pyrazine-2-carboxamidine hydrochloride (0.62 g, 3.9 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.0026 g, 2% yield). Mp = 212-214°C. MS (M + 1) = 450 m/z.

Example 42



Compound 39



Compound 40

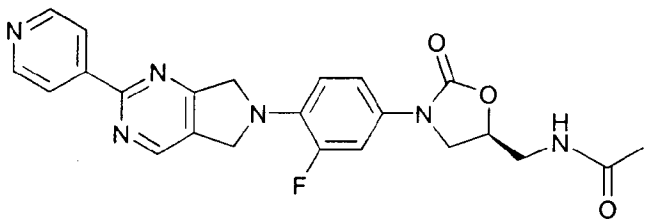
The above acetamide from Example 39 (0.040 g, 0.088 mmols) was taken up in CH_2Cl_2 (10 mL) and MnO_2 (0.36 g, 3.5 mmols) added in three portions over three days. After stirring for three days the reaction mixture was filtered through Celite, concentrated and chromatography on silica with 7%

$MeOH/CH_2Cl_2$ as eluent. Two products were isolated from the chromatography: 0.001 g of Compound 39 as a light yellow solid (4% yield); and 0.002 g of Compound 40 as a yellow solid (4% yield).

Compound 39: MS (M + 1) = 448 m/z.

Compound 40: MS (M + 1) = 464 m/z.

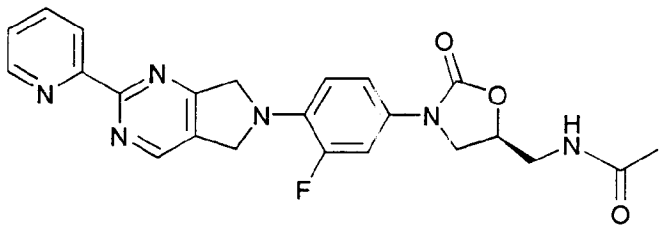
Example 43



Compound 41

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and 4-amidinopyridine hydrochloride (0.81 g, 5.2 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% $MeOH/CH_2Cl_2$ as eluent to afford the product as a light yellow solid (0.072 g, 55% yield). Mp = 245-250°C, decomp. MS (M + 1) = 449 m/z.

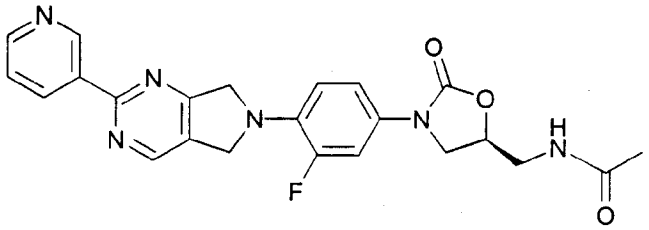
Example 44



Compound 42

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (1 mL) and 2-amidinopyridine hydrochloride (0.61 g, 3.9 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a yellow powder (0.054 g, 40% yield). Mp = 216-220°C. MS (M + 1) = 449 m/z.

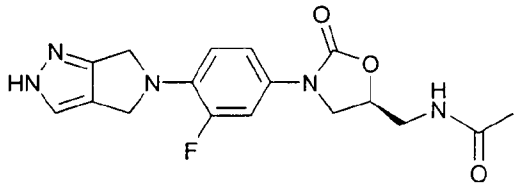
Example 45



Compound 43

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and 3-amidinopyridine hydrochloride (0.49 g, 3.1 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light purple, crystalline solid (0.044 g, 33% yield). Mp = 265-270°C, decomp. MS (M + 1) = 449 m/z.

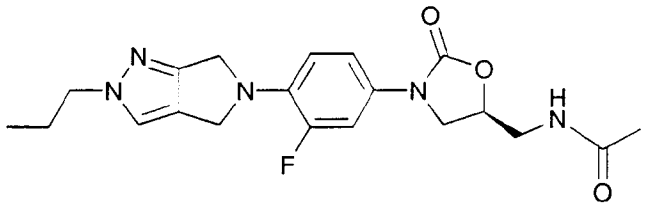
Example 46



Compound 44

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and hydrazine hydrochloride (0.22 g, 3.2 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as off-white powder (0.022 g, 21% yield). Mp = 244-247°C, decomp. MS (M + 1) = 360 m/z.

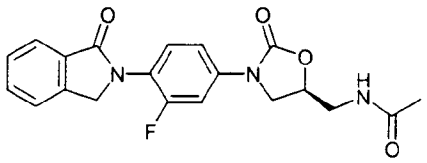
Example 47



Compound 45

To the β-ketoenamine (prepared as in Example 39) was added benzene (5 mL), DMF (2 mL) and n-propylhydrazine oxalate (0.87 g, 5.3 mmols). After heating overnight at 95°C the reaction mixture was cooled to rt and water (8 mL) was added. A ppt formed and was collected by filtration, dried in a vacuum oven (50°C), and chromatographed on silica with 5% MeOH/CH_2Cl_2 as eluent to afford the product as a light yellow solid (0.081 g, 55% yield). Mp = 204-208°C. MS (M + 1) = 402 m/z.

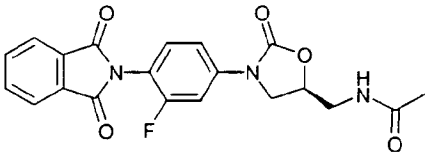
Example 48



Compound 46

The starting material aniline (N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide) was prepared as in World Patent WO 96/23788. To phthalic dicarboxaldehyde (0.0522 g, 0.378 mmol) in acetonitrile (1 mL) was added glacial acetic acid (0.05 mL, 0.87 mmol) and then the above aniline (0.0955 g, 0.357 mmol) in acetonitrile (5 mL) dropwise. After 4 hrs water (10 mL) was added and a precipitate was collected on a filter and washed with water and ether to provide Compound 46 as a light green solid (0.0655g, 48%). Mp = 211-214 °C. MS (M + 1) = 384 m/z.

Example 49

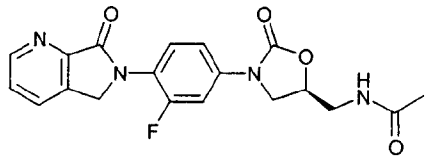


Compound 47

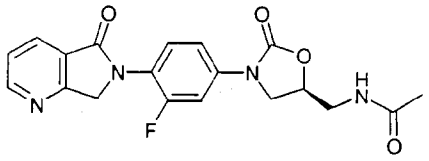
To starting material aniline (N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide)(0.095 g, 0.36 mmol)(as prepared in World Patent WO 96/23788) in CH_2Cl_2 (5 mL) was added triethylamine (0.15 mL, 1.1 mmols) and phthaloyl dichloride (0.056 mL, 0.39 mmol). After stirring overnight a solid was collected on a filter, washed with water (10 mL) and

dried in vacuum oven (50°C) to afford the product as a off-white solid (0.060, 42%). Mp = 240-242°C. MS (M + 1) = 398 m/z.

Example 50



Compound 48



Compound 49

To starting material aniline (N-[[(5S)-3-(4-amino-3-fluorophenyl)-2-oxo-5-oxazolidinyl]methyl]-acetamide)(0.20 g, 0.75 mmol)(as prepared in World Patent WO 96/23788) in acetonitrile (5 mL) was added 2,3-pyridine dicarboxaldehyde (0.10 g, 6.6 mmols) and glacial acetic acid (0.050 mL, 0.87 mmol). After stirring for 5hrs the reaction mixture was concentrated and chromatographed on silica with 2.5% MeOH/CH_2Cl_2 as eluent to afford the two products: 0.035 g of Compound 52 (12%) as a yellow solid; and 0.011 g of Compound 53 (4%) as a yellow solid.

Compound 48: Mp = 230-232°C. MS (M + 1) = 385 m/z.

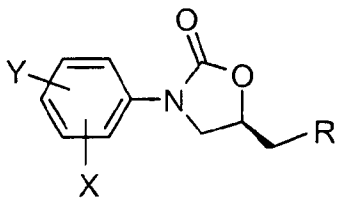
Compound 49: Mp = 207-209°C. MS (M + 1) = 385 m/z.

The invention has been described in detail with particular reference to the above embodiments thereof. The above embodiments and examples are given to illustrate the scope and spirit of the present invention. These embodiments and examples will make apparent, to those skilled in the art, other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. It will be understood that variations and modifications can be effected within the spirit and scope of the invention; therefore, the instant invention should be limited only by the appended claims.

CLAIMS

We claim:

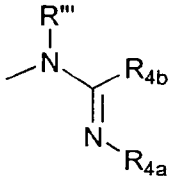
1. A compound of Formula I



Formula I

wherein:

R is selected from the group consisting of OH, O-Aryl, O-Heteroaryl, N_3, OR', OSO_2R'', -NR'''R'''', or



wherein:

(i) R' is straight-chain or branched acyl having up to 6 carbon atoms or benzyl;

(ii) R'' is straight-chain or branched alkyl, having up to 5 carbon atoms, phenyl or tolyl; and

(iii) R''' and R'''' are independently selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, phenyl or tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by cyano or alkoxycarbonyl having up to 4 carbon atoms, $-CO_2-R_1$, $-CO-R_1$, $-CO-SR_1$, $-CS-R_1$, $P(O)(OR_2)(OR_3)$, and $-SO_2-R_4$, in which

R_1 is selected from the group consisting of H, cycloalkyl having 3 to 6 carbon atoms, trifluoromethyl or phenyl, benzyl\ or acyl having up to 5 carbon atoms, straight-chain or branched alkyl having up to 6 carbon

55

atoms, said alkyl optionally substituted by straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms, OH, cyano, up to 3 halogen atoms, and -NR_5 R_6 in which R_5 and R_6 are identical or different and are selected from H, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms;

R_2 and R_3 are identical or different and are selected from hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms; and

R_4 is selected from straight-chain or branched alkyl having up to 4 carbon atoms or phenyl and;

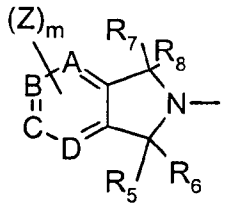
R_{4a} is CN, COR_{4c}, $COOR_{4c}$, $CONHR_{4c}$, CO-NR_{4c} R_{4d}, SO_2R_{4c}, SO_2NHR_{4c}, SO_2-NR_{4c} R_{4d}, or NO_2;

R_{4b} is H, alkyl, OR_{4c}, SR_{4c}, amino, NHR_{4c}, NR_{4c},R_{4d}, (C1-C8), alkylaryl or mono-, di-, tri-, and per-halo(C1-C8) alkyl;

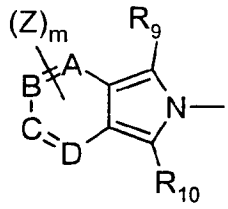
R_{4c} and R_{4d} are independently selected from H, alkyl, aryl, or in the case of any $NR_{4c}R_{4d}$ group R_{4c} and R_{4d} taken together with the nitrogen atom to which they are attached form a unsubstituted or substituted pyrrolidinyl, piperidinyl or morpholinyl group;

X is 0 to 4 members independently selected from the group consisting of halogen, OH, mercapto, nitro, halo-C_{1-8}-alkyl, C_{1-8} alkoxy, thio-C_{1-8}-alkyl, C_{1-8} alkyl-amino, di(C_{1-8}-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8} alkyl-CO-O-, C_{1-8} alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, amine, C_{3-6} cycloalkyl, C_{1-8} alkyl optionally substituted with one or more members selected from the group consisting of F, Cl, OH, C_{1-8} alkoxyl and C_{1-8} acyloxy; and

Y is a radical of Formulae II or III:



Formula II



Formula III

wherein

R_5, R_6, R_7, and R_8 are each independently H, alkyl, CN, nitro, C_{1-8} alkyl, halo-C_{1-8}-alkyl, formyl, carboxy, alkoxycarbonyl, carboxamide, aryl, substituted-aryl, heteroaryl, or substituted-heteroaryl, or R_5 and R_6 and/or R_7 and R_8 together form an oxo group;

R_9, and R_{10} are each independently H, halogen, alkyl, OH, CN, mercapto, nitro, C_{1-8} alkyl, halo-C_{1-8}-alkyl, C_{1-8} alkoxyl, thio-C_{1-8}-alkyl, amino, C_{1-8}-alkyl-amino, di(C_{1-8}-alkyl-)amino, formyl, carboxy, alkoxycarbonyl, C_{1-8}-alkyl-CO-O-, C_{1-8}-alkyl-CO-NH-, carboxamide, aryl, substituted-aryl, alkoxy, heteroaryl, substituted-heteroaryl, or amine ;

A, B, C, and D are selected from C, S, O, and N to form any five to ten membered aromatic or heteroaromatic ring, said heteroaromatic ring having one to four members selected from the group consisting of S, O, and N;

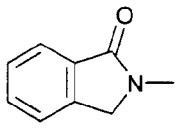
Z is selected from halogen, alkyl, aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, CN, CHO, COalkyl, amine, (dialkylamino)alkyl where dialkylamino is selected from dimethylamine, diethylamine,

morpholinyl, thiomorpholinyl, pyrroidinyl, or piperidinyl, or, alkoxy, or NHCO-(C_1-C_8-alkyl); and

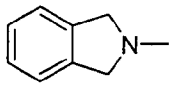
m is 0 or 1,

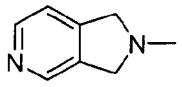
and the pharmaceutically acceptable salts and esters thereof.

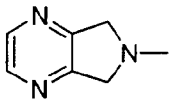
2. The compound of claim 1 wherein Y is selected from the group consisting of

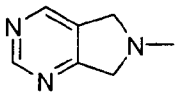


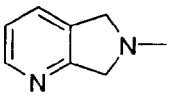
isoindolone-;

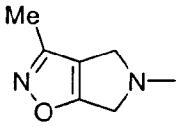

(1,3-dihydro-2H-isoindol-2-yl)-;

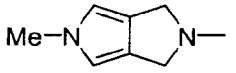

(6,7-dihydro-5H-pyrrolo[3,4-*c*]pyridin-6-yl)-;

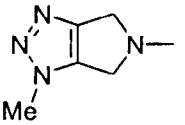

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyrazin-6-yl)-;

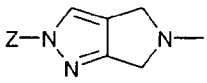

(6,7-dihydro-5H-pyrrolo[3,4-*d*]pyrimidin-6-yl)-;

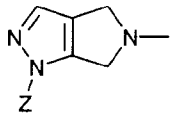

(5,7-dihydro-6H-pyrrolo[3,4-*b*]pyridin-6-yl)-;


(4,6-dihydro-3-methyl-5H-pyrrolo[3,4-*d*]isoxazol-5-yl)-;

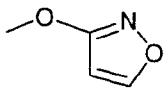

(3,5-dihydro-5-methylpyrrolo[3,4-*c*]pyrrol-2(1H)-yl)-; and

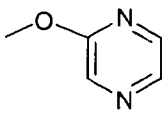

(4,6-dihydro-1-methylpyrrolo[3,4-*d*]-1,2,3-triazol-5(1H)-yl)-.

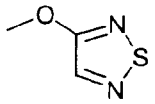


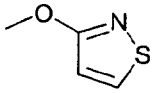


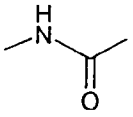
3. The compound of claim 1 wherein R is -NHCOCH$_3$ or is selected from the group consisting of

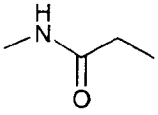


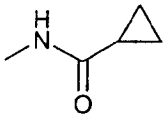


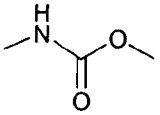


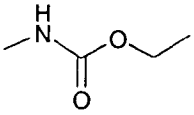


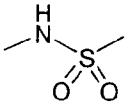


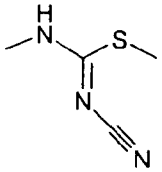


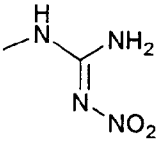






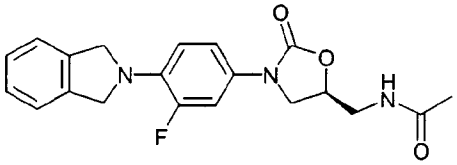






5

4. A compound of Claim 1 having the formula:



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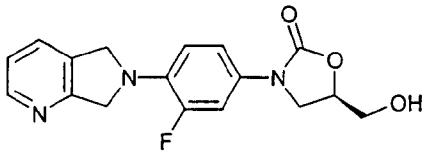
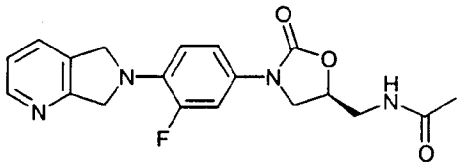
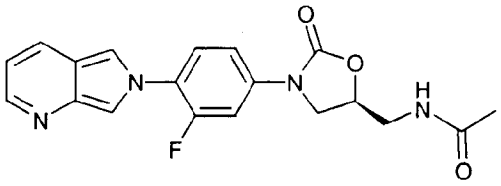


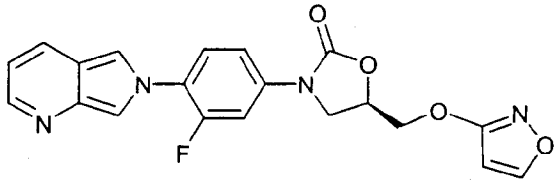
6. A compound of Claim 1 having the formula:



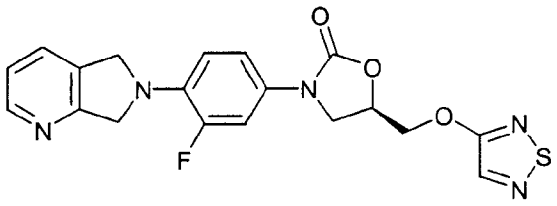
7. A compound of Claim 1 having the formula:



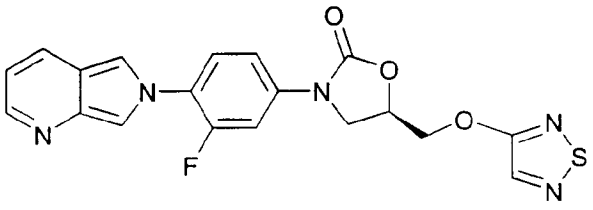
8. A compound of Claim 1 having the formula:



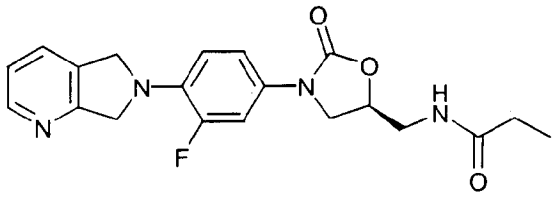
9. A compound of Claim 1 having the formula:\



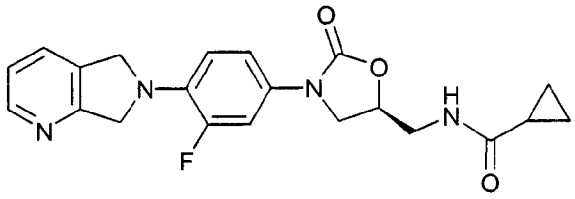
10. A compound of Claim 1 having the formula:



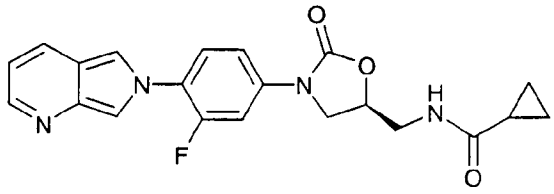
11. A compound of Claim 1 having the formula:



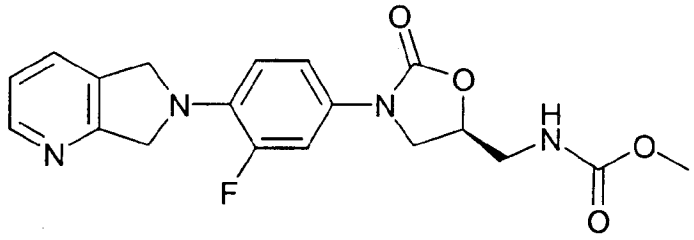
12. A compound of Claim 1 having the formula:



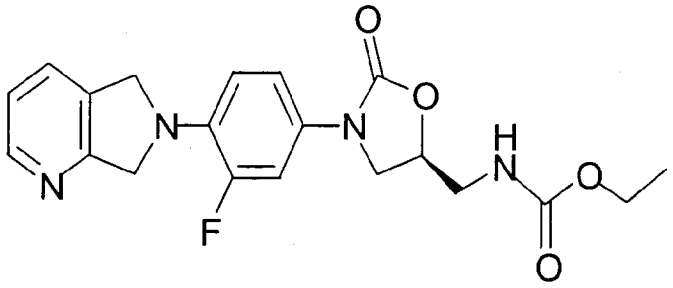
13. A compound of Claim 1 having the formula:



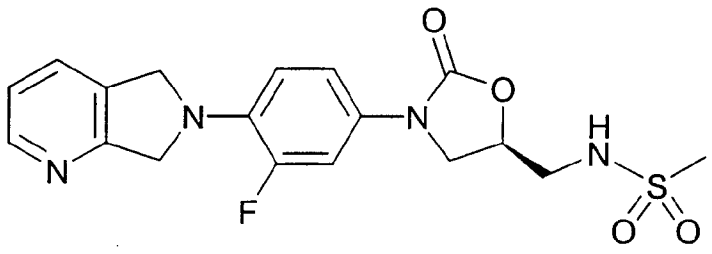
14. A compound of Claim 1 having the formula:



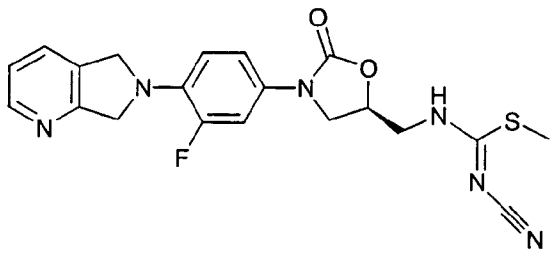
15. A compound of Claim 1 having the formula:



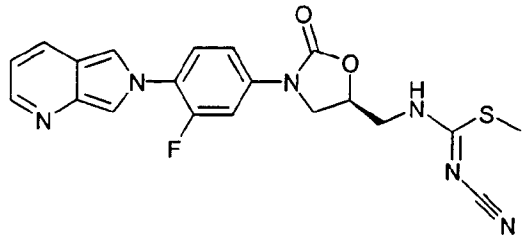
16. A compound of Claim 1 having the formula:



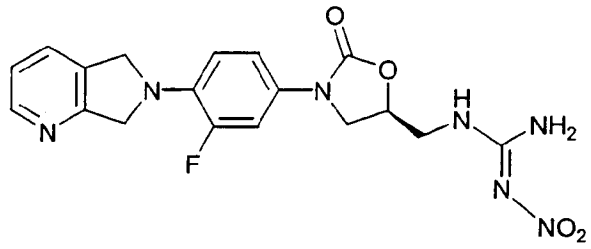
17. A compound of Claim 1 having the formula:



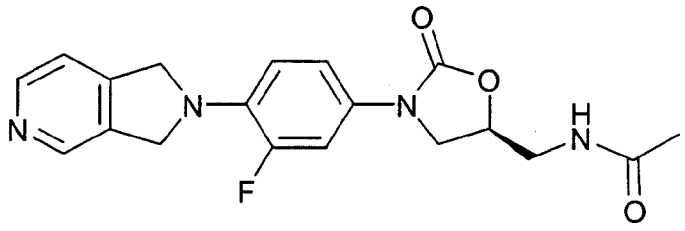
18. A compound of Claim 1 having the formula:



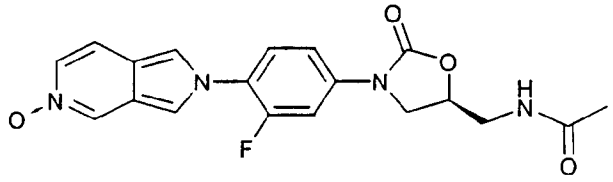
19. A compound of Claim 1 having the formula:



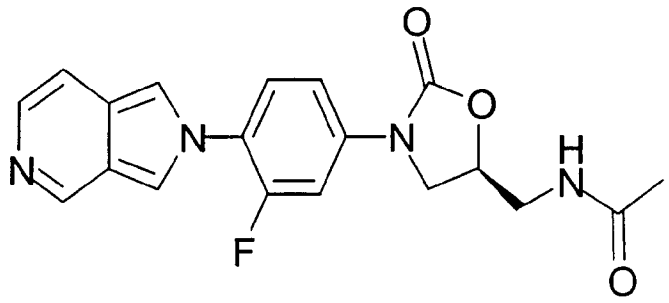
20. A compound of Claim 1 having the formula:



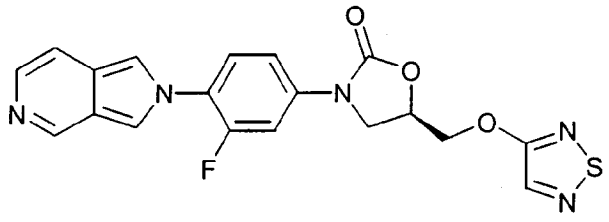
21. A compound of Claim 1 having the formula:



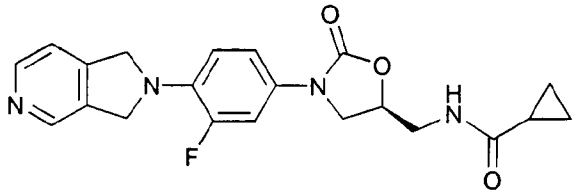
22. A compound of Claim 1 having the formula:



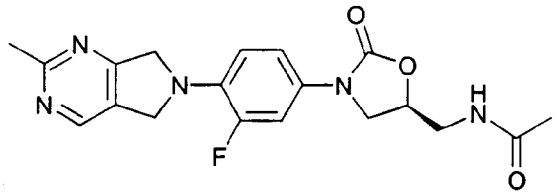
23. A compound of Claim 1 having the formula:



24. A compound of Claim 1 having the formula:



25. A compound of Claim 1 having the formula:



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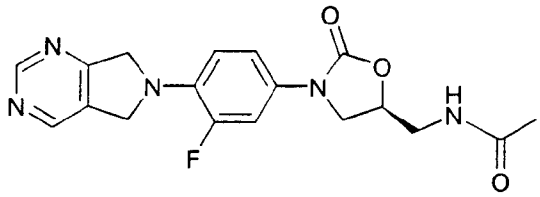

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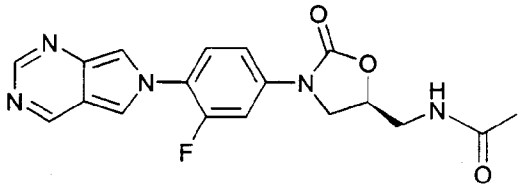
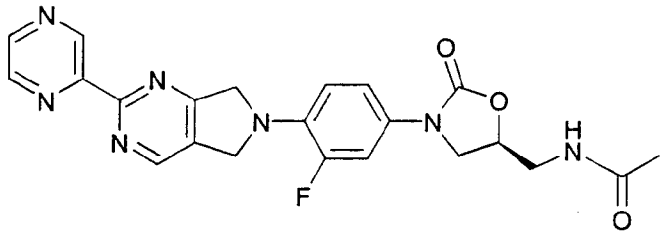


28. A compound of Claim 1 having the formula:



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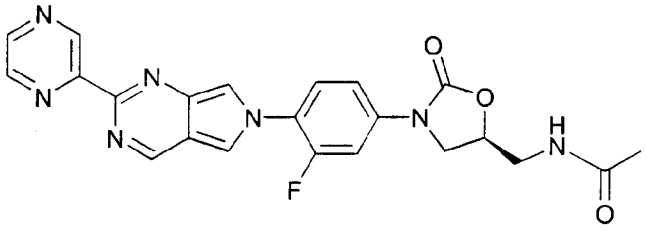

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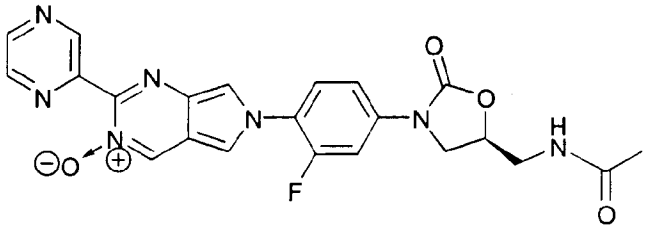
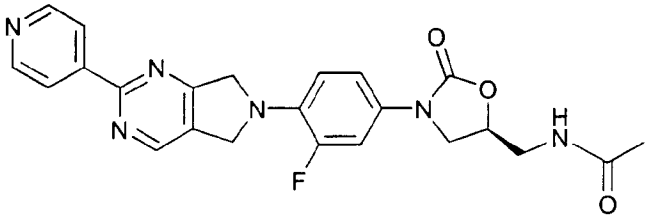


31. A compound of Claim 1 having the formula:



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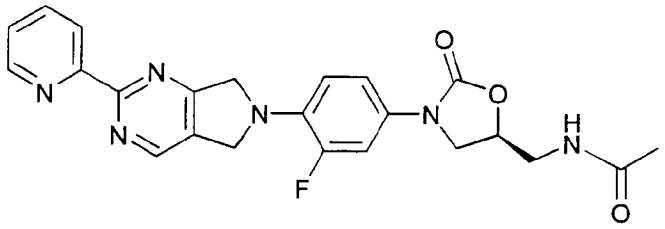
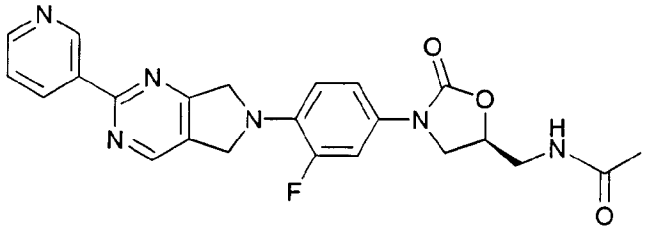
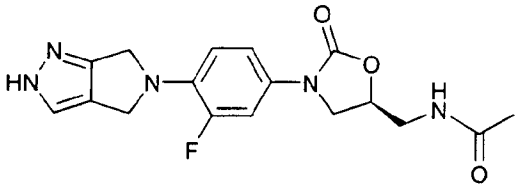


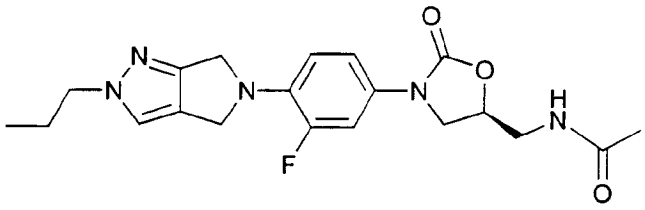
33. A compound of Claim 1 having the formula:



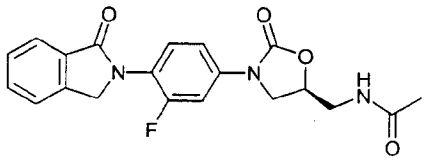
34. A compound of Claim 1 having the formula:



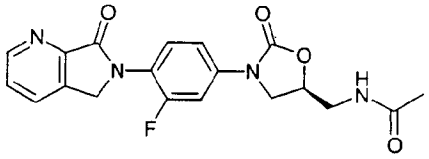
35. A compound of Claim 1 having the formula:



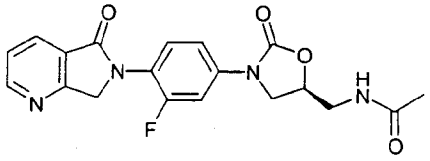
36. A compound of Claim 1 having the formula:



37. A compound of Claim 1 having the formula:



38. A compound of Claim 1 having the formula:



39. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

40. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said mammal a therapeutically effective amount of the compound according to Claim 1.

41. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective dose of the pharmaceutical composition of a compound according to Claim 1.

42. The method of Claim 40 or 41 wherein said condition is selected from the group consisting of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, bone and joint infections and hospital-acquired lung infections.

43. The method of Claim 40 or 41 wherein said bacterium is selected from the group consisting of *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes*, *Enterococcus spp.*, *Moraxella catarrhalis* and *H. influenzae*.

44. The method of Claim 40 or 41 wherein said bacterium is a Gram-positive coccus.

45. The method of Claim 44 wherein said Gram-positive coccus is drug-resistant.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/21093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/10 C07D471/04 C07D487/04 C07D498/04 A61K31/422
A61K31/437 A61K31/4985 A61K31/519 A61K31/424 A61P31/04
//(C07D471/04,221:00,209:00),(C07D487/04,231:00,209:00),

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 7 C07D A61K A61P

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)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	DATABASE WPI Section Ch, Week 200006 Derwent Publications Ltd., London, GB; Class B03, AN 2000-069004 XP002154332 -& JP 11 322729 A (HOKURIKU PHARM CO LTD), 24 November 1999 (1999-11-24) abstract; particularly page 43, no 130, page 51, no 170, page 60, no 212, page 75, no 278 and page 88, no 56 of the original document	1-45
Y	WO 96 23788 A (PHARMACIA + UPJOHN COMPANY) 8 August 1996 (1996-08-08) cited in the application the whole document	1-45

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	14/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allard, M

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Form PCT/ISA/210 (second sheet) (July 1992)

0442

INTERNATIONAL SEARCH REPORT

Interl ..nal Application No
PCT/US 00/21093

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 (C07D487/04,241:00,209:00),(C07D498/04,261:00,209:00), (C07D487/04,209:00,209:00),(C07D487/04,249:00,209:00), (C07D487/04,239:00,209:00)

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)

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.
A	WO 99 10342 A (ZENECA LIMITED) 4 March 1999 (1999-03-04) the whole document	1,39-45
A	WO 96 35691 A (PHARMACIA & UPJOHN COMPANY) 14 November 1996 (1996-11-14) the whole document	1,39-45
A	WO 96 15130 A (THE UPJOHN COMPANY) 23 May 1996 (1996-05-23) the whole document	1,39-45

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

☒ Patent family members are listed in annex.

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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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Allard, M

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Form PCT/ISA/210 (second sheet) (July 1992)

0443

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten ›nal Application No
PCT/US 00/21093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 11322729 A	24-11-1999	NONE	
WO 9623788 A	08-08-1996	AU 703465 B	25-03-1999
		AU 4899896 A	21-08-1996
		BR 9607017 A	28-10-1997
		CA 2208603 A	08-08-1996
		CN 1172484 A	04-02-1998
		CZ 9702314 A	12-08-1998
		EP 0807112 A	19-11-1997
		FI 973217 A	04-08-1997
		JP 10513446 T	22-12-1998
		NO 973550 A	03-10-1997
		NZ 302844 A	29-06-1999
		PL 321663 A	22-12-1997
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WO 9910342 A	04-03-1999	EP 1005468 A	07-06-2000
WO 9635691 A	14-11-1996	AU 702752 B	04-03-1999
		AU 5484996 A	29-11-1996
		CA 2218088 A	14-11-1996
		CN 1184481 A	10-06-1998
		EP 0828741 A	18-03-1998
		FI 974180 A	10-11-1997
		JP 11506430 T	08-06-1999
		NO 975158 A	09-01-1998
		US 6090820 A	18-07-2000
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		EP 0792273 A	03-09-1997
		JP 10508844 T	02-09-1998
		NO 972222 A	14-05-1997
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(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
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(74) Gemeinsamer Vertreter: **BAYER AKTIENGESELLSCHAFT**; 51368 Leverkusen (DE).

(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

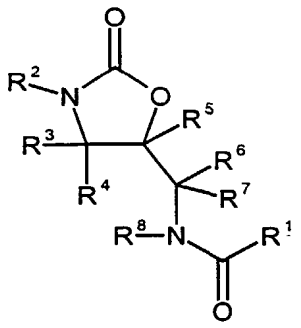
(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *Mit internationalem Recherchenbericht.*
— *Vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen.*

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** SUBSTITUTED OXAZOLIDINONES AND THEIR USE IN THE FIELD OF BLOOD COAGULATION

(54) **Bezeichnung:** SUBSTITUIERTE OXAZOLIDINONE UND IHRE VERWENDUNG IM GEBIET DER BLUTGERINNUNG



(I)

(57) **Abstract:** The invention relates to the field of blood coagulation, more specifically it relates to novel oxazolidinone derivatives of the general formula (I), to methods for producing them as well as to their use as active substances for medicaments for the prophylaxis and/or the treatment of diseases.

(57) **Zusammenfassung:** Die Erfindung betrifft das Gebiet der Blutgerinnung. Es werden neue Oxazolidinonderivate der allgemeinen Formel (I), Verfahren zu ihrer Herstellung sowie ihre Verwendung als Arzneimittelwirkstoffe zur Prophylaxe und/oder Behandlung von Erkrankungen beschrieben.

WO 01/47919 A1

SUBSTITUIERTE OXAZOLIDINONE UND IHRE VERWENDUNG IM GEBIET DER BLUTGERINNUNG

Die vorliegende Erfindung betrifft das Gebiet der Blutgerinnung. Insbesondere betrifft die vorliegende Erfindung neue Oxazolidinon-Derivate, Verfahren zu ihrer Herstellung sowie ihre Verwendung als Wirkstoffe in Arzneimitteln.

Die Blutgerinnung ist ein Schutzmechanismus des Organismus, mit dessen Hilfe Defekte in der Gefäßwand rasch und zuverlässig „abgedichtet" werden können. So kann ein Blutverlust vermieden bzw. minimiert werden. Die Blutstillung nach Gefäßverletzung erfolgt im wesentlichen durch das Gerinnungssystem, bei dem eine enzymatische Kaskade komplexer Reaktionen von Plasmaproteinen ausgelöst wird. Hierbei sind zahlreiche Blutgerinnungsfaktoren beteiligt, von denen jeder, sobald aktiviert, die jeweils nächste inaktive Vorstufe in ihre aktive Form überführt. Am Ende der Kaskade steht die Umwandlung des löslichen Fibrinogens in das unlösliche Fibrin, so dass es zu einem Blutgerinnsel kommt. Traditionell unterscheidet man bei der Blutgerinnung zwischen dem intrinsischen und extrinsischen System, die in einem abschließenden gemeinsamen Reaktionsweg münden. Hierbei kommt dem Faktor Xa, der aus dem Proenzym Faktor X gebildet wird, eine Schlüsselrolle zu, da er beide Gerinnungswege verbindet. Die aktivierte Serinprotease Xa spaltet Prothrombin zu Thrombin. Das entstandene Thrombin wiederum spaltet seinerseits Fibrinogen zu Fibrin, einem faserig-gallertigem Gerinnungsstoff. Darüber hinaus ist Thrombin ein potenter Auslöser der Thrombozytenaggregation, die ebenfalls einen erheblichen Beitrag bei der Hämostase leistet.

Die Aufrechterhaltung der normalen Hämostase - zwischen Blutung und Thrombose - unterliegt einem komplexen Regulationsmechanismus. Die unkontrollierte Aktivierung des Gerinnungssystems oder eine defekte Hemmung der Aktivierungsprozesse kann die Bildung von lokalen Thromben oder Embolien in Gefäßen (Arterien, Venen, Lymphgefäßen) oder Herzhöhlen bewirken. Dies kann zu schwerwiegenden Erkrankungen wie Herzinfarkt, Angina Pectoris (eingeschlossen instabile Angina), Reokklusionen und Restenosen nach einer Angioplastie oder aortokoro-

narem Bypass, Hirnschlag, transitorische ischämische Attacken, periphere arterielle Verschlusskrankheiten, Lungenembolien oder tiefen venösen Thrombosen führen; diese Erkrankungen werden im folgenden zusammenfassend auch als thromboembolische Erkrankungen bezeichnet. Darüber hinaus kann eine Hyperkoagulabilität - systemisch - bei einer Verbrauchskoagulopathie zur disseminierten intravasalen Gerinnung führen.

Diese thromboembolischen Erkrankungen sind die häufigste Ursache von Morbidität und Mortalität in den meisten industrialisierten Ländern (Pschyrembel, Klinisches Wörterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, Seite 199 ff., Stichwort „Blutgerinnung"; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort „Blutgerinnung"; Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, Seiten 259 ff.).

Die aus dem Stand der Technik bekannten Antikoagulantien, d.h. Stoffe zur Hemmung oder Verhinderung der Blutgerinnung, weisen verschiedene, oftmals gravierende Nachteile auf. Eine effiziente Behandlungsmethode bzw. Prophylaxe von thromboembolischen Erkrankungen erweist sich in der Praxis deshalb als sehr schwierig und unbefriedigend.

Für die Therapie und Prophylaxe von thromboembolischen Erkrankungen findet zum einen Heparin Verwendung, das parenteral oder subkutan appliziert wird. Aufgrund günstigerer pharmakokinetischer Eigenschaften wird zwar heutzutage zunehmend niedermolekulares Heparin bevorzugt; allerdings können auch hierdurch die im folgenden geschilderten bekannten Nachteile nicht vermieden werden, die bei der Therapierung mit Heparin bestehen. So ist Heparin oral unwirksam und besitzt nur eine vergleichsweise geringe Halbwertszeit. Da Heparin gleichzeitig mehrere Faktoren der Blutgerinnungskaskade hemmt, kommt es zu einer unselektiven Wirkung. Darüber hinaus besteht ein hohes Blutungsrisiko, insbesondere können Hirnblutungen und Blutungen im Gastrointestinaltrakt auftreten, und es kann zu Thrombopenie, Alopecia medicomentosa oder Osteoporose kommen (Pschyrembel, Klinisches

Wörterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, Seite 610, Stichwort „Heparin"; Römpp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort „Heparin").

Eine zweite Klasse von Antikoagulantien stellen die Vitamin K-Antagonisten dar. Hierzu gehören beispielsweise 1,3-Indandione, vor allem aber Verbindungen wie Warfarin, Phenprocoumon, Dicumarol und andere Cumarin-Derivate, die unselektiv die Synthese verschiedener Produkte bestimmter Vitamin K-abhängiger Gerinnungsfaktoren in der Leber hemmen. Durch den Wirkmechanismus bedingt, setzt die Wirkung aber nur sehr langsam ein (Latenzzeit bis zum Wirkeintritt 36 bis 48 Stunden). Die Verbindungen können zwar oral appliziert werden, aufgrund des hohen Blutungsrisikos und des engen therapeutischen Indexes ist aber eine aufwendige individuelle Einstellung und Beobachtung des Patienten notwendig. Darüber hinaus sind weitere Nebenwirkungen wie gastrointestinale Störungen, Haarausfall und Hautnekrosen beschrieben (Pschyrembel, Klinisches Wörterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, Seite 292 ff., Stichwort „Cumarinderivate"; Ullmann's Encyclopedia of Industrial Chemistry, 5. Auflage, VCH Verlagsgesellschaft, Weinheim, 1985 - 1996, Stichwort „Vitamin K").

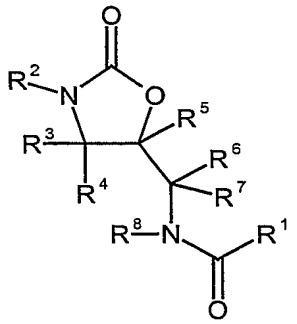
In jüngster Zeit ist ein neuer Therapieansatz für die Behandlung und Prophylaxe von thromboembolischen Erkrankungen beschrieben worden. Ziel dieses neuen Therapieansatzes ist die Inhibierung von Faktor Xa (vgl. WO-A-99/37304; WO-A-99/06371; J. Hauptmann, J. Stürzebecher, Thrombosis Research **1999**, *93*, 203; F. Al-Obeidi, J. A. Ostrem, Factor Xa inhibitors by classical and combinatorial chemistry, DDT **1998**, *3*, 223; F. Al-Obeidi, J. A. Ostrem, Factor Xa inhibitors, Exp. Opin. Ther. Patents **1999**, *9*, 931; B. Kaiser, Thrombin and factor Xa inhibitors, Drugs of the Future **1998**, *23*, 423; A. Uzan, Antithrombotic agents, Emerging Drugs **1998**, *3*, 189; B.-Y. Zhu, R. M. Scarborough, Curr. Opin. Card. Pulm. Ren. Inv. Drugs **1999**, *1 (1)*, 63). Dabei ist gezeigt worden, dass verschiedene, sowohl peptidische wie nichtpeptidische Verbindungen in Tiermodellen als Faktor Xa-Inhibitoren wirksam sind.

Aufgabe der vorliegenden Erfindung ist nunmehr die Bereitstellung neuer Substanzen zur Bekämpfung von Erkrankungen, die eine große therapeutische Bandbreite aufweisen.

Sie sollen insbesondere zur effizienteren Prophylaxe und/oder Behandlung von thromboembolischen Erkrankungen geeignet sein und hierbei die zuvor geschilderten Nachteile des Standes der Technik – zumindest teilweise – vermeiden, wobei unter dem Begriff „thromboembolische Erkrankungen" im Sinne der vorliegenden Erfindung insbesondere schwerwiegende Erkrankungen wie Herzinfarkt, Angina Pectoris (eingeschlossen instabile Angina), Reokklusionen und Restenosen nach einer Angioplastie oder aortokoronarem Bypass, Hirnschlag, transitorische ischämische Attacken, periphere arterielle Verschlusskrankheiten, Lungenembolien oder tiefe venöse Thrombosen verstanden werden.

Weitere Aufgabe der vorliegenden Erfindung ist die Bereitstellung neuer Antikoagulantien, welche mit erhöhter Selektivität den Blutgerinnungsfaktor Xa inhibieren und hierbei die Probleme der aus dem Stand der Technik bekannten Therapiemethoden für thromboembolische Erkrankungen – zumindest teilweise – vermeiden sollen.

Gegenstand der vorliegenden Erfindung sind somit substituierte Oxazolidinone der allgemeinen Formel (I)



(I),

in welcher:

R^1 für gegebenenfalls benzokondensiertes Thiophen (Thienyl) steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann;

R^2 für einen beliebigen organischen Rest steht;

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

sowie deren pharmazeutisch verträglichen Salze, Hydrate und Prodrugs,

ausgenommen jedoch Verbindungen der allgemeinen Formel (I), bei denen der Rest R^1 ein unsubstituierter 2-Thiophenrest ist und gleichzeitig der Rest R^2 einen ein- oder mehrfach substituierten Phenylrest darstellt und gleichzeitig die Reste R^3, R^4, R^5, R^6, R^7 und R^8 jeweils Wasserstoff bedeuten.

Bevorzugt sind hierbei Verbindungen der allgemeinen Formel (I),

worin

R^1 für gegebenenfalls benzokondensiertes Thiophen (Thienyl) steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch einen Rest aus der Gruppe von Halogen; Cyano; Nitro; Amino; Aminomethyl; (C_1-C_8)-Alkyl, das gegebenenfalls seinerseits ein- oder mehrfach durch Halogen substituiert sein kann; (C_3-C_7)-Cycloalkyl; (C_1-C_8)-Alkoxy; Imidazolinyl; -C(=NH)NH_2; Carbamoyl; und Mono- und Di-(C_1-C_4)-alkyl-aminocarbonyl,

R^2 für eine der folgenden Gruppen steht:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,

B-M-B-,

D-M-B-,

wobei:

der Rest „A“ für (C_6-C_{14})-Aryl, vorzugsweise für (C_6-C_{10})-Aryl, insbesondere für Phenyl oder Naphthyl, ganz besonders bevorzugt für Phenyl, steht;

der Rest „B“ für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 3 Heteroatome und/oder Hetero-Kettenglieder, insbesondere bis zu 2 Heteroatome und/oder Hetero-Kettenglieder, aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D“ für einen gesättigten oder teilweise ungesättigten, mono- oder bicyclischen, gegebenenfalls benzokondensierten 4- bis 9-gliedrigen Heterocyclus steht, der bis zu drei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;

der Rest „M“ für –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- , -SO_2- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A“, „B“ und „D“ jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Nitro; Carbamoyl; Pyridyl; (C_1-C_6)-Alkanoyl; (C_3-C_7)-Cycloalkanoyl; (C_6-C_{14})-Arylcarbonyl; (C_5-C_{10})-Heteroarylcarbonyl; (C_1-C_6)-Alkanoyloxymethyloxy; (C_1-C_4)-Hydroxyalkylcarbonyl; -$COOR^{27}$; -SO_2R^{27}; -$C(NR^{27}R^{28})=NR^{29}$; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OR^{30}; -$NR^{30}R^{31}$, (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl,

wobei (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; $-OR^{27}$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ und $-C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1 bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkanoyl, Carbamoyl, Trifluormethyl, Phenyl oder Pyridyl bedeuten,
und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu drei, vorzugsweise bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, $-CH_2C(NR^{27}R^{28})=NR^{29}$ oder $-COR^{33}$ bedeuten,

wobei

R^{33} (C_1-C_6)-Alkoxy, (C_1-C_4)-Alkoxy-(C_1-C_4)-alkyl, (C_1-C_4)-Alkoxycarbonyl-(C_1-C_4)-alkyl, (C_1-C_4)-Aminoalkyl, (C_1-C_4)-Alkoxycarbonyl, (C_1-C_4)-Alkanoyl-(C_1-C_4)-alkyl, (C_3-C_7)-Cycloalkyl, (C_2-C_6)-Alkenyl, (C_1-C_8)-Alkyl, das gegebenenfalls durch Phenyl oder Acetyl substituiert sein kann, (C_6-C_{14})-Aryl, (C_5-C_{10})-Heteroaryl, Trifluormethyl, Tetrahydrofuranyl oder Butyrolacton bedeutet,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze, Hydrate und Prodrugs,

ausgenommen jedoch Verbindungen der allgemeinen Formel (I), bei denen der Rest R^1 ein unsubstituierter 2-Thiophenrest ist und gleichzeitig der Rest R^2 einen ein- oder mehrfach substituierten Phenylrest darstellt und gleichzeitig die Reste R^3, R^4, R^5, R^6, R^7 und R^8 jeweils Wasserstoff bedeuten.

Ebenfalls bevorzugt sind hierbei Verbindungen der allgemeinen Formel (I),

worin

R^1 für Thiophen (Thienyl), insbesondere 2-Thiophen, steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch Halogen, vorzugsweise Chlor oder Brom, Amino, Aminomethyl oder (C_1-C_8)-Alkyl, vorzugsweise Methyl, wobei der (C_1-C_8)-Alkylrest gegebenenfalls seinerseits ein- oder mehrfach durch Halogen, vorzugsweise Fluor, substituiert sein kann,

R^2 für eine der folgenden Gruppen steht:

A-,

A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

wobei:

der Rest „A" für (C_6-C_{14})-Aryl, vorzugsweise für (C_6-C_{10})-Aryl, insbesondere für Phenyl oder Naphthyl, ganz besonders bevorzugt für Phenyl, steht;
der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 3 Heteroatome und/oder Hetero-Kettenglieder, insbesondere bis zu 2 Heteroatome und/oder Hetero-Kettenglieder, aus der Reihe S, N, NO (N-Oxid) und O enthält;
der Rest „D" für einen gesättigten oder teilweise ungesättigten 4- bis 7-gliedrigen Heterocyclus steht, der bis zu drei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;
der Rest „M" für –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- oder für eine kovalente Bindung steht;

wobei
die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Nitro; Carbamoyl; Pyridyl; (C_1-C_6)-Alkanoyl; (C_3-C_7)-Cycloalkanoyl; (C_6-C_{14})-Arylcarbonyl; (C_5-C_{10})-Heteroarylcarbonyl; (C_1-C_6)-Alkanoyloxy-

methyloxy; -$COOR^{27}$; -SO_2R^{27}; -$C(NR^{27}R^{28})=NR^{29}$; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OR^{30}; -$NR^{30}R^{31}$, (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl,

wobei (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; -OR^{27}; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ und -$C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1 bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeuten,
und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu drei, vorzugsweise bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_4)-Alkanoyl, (C_6-C_{14})-Arylcarbonyl, (C_5-C_{10})-Heteroarylcarbonyl, (C_1-C_4)-Alkylaminocarbonyl oder -$CH_2C(NR^{27}R^{28})=NR^{29}$ bedeuten,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze, Hydrate und Prodrugs,

ausgenommen jedoch Verbindungen der allgemeinen Formel (I), bei denen der Rest R^1 ein unsubstituierter 2-Thiophenrest ist und gleichzeitig der Rest R^2 einen ein- oder mehrfach substituierten Phenylrest darstellt und gleichzeitig die Reste R^3, R^4, R^5, R^6, R^7 und R^8 jeweils Wasserstoff bedeuten.

Besonders bevorzugt sind hierbei Verbindungen der allgemeinen Formel (I),

worin

R^1 für Thiophen (Thienyl), insbesondere 2-Thiophen, steht, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch Halogen, vorzugsweise Chlor oder Brom, oder (C_1-C_8)-Alkyl, vorzugsweise Methyl, wobei der (C_1-C_8)-Alkylrest gegebenenfalls seinerseits ein- oder mehrfach durch Halogen, vorzugsweise Fluor, substituiert sein kann,

R^2 für eine der folgenden Gruppen steht:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

wobei:

der Rest „A“ für Phenyl oder Naphthyl, insbesondere für Phenyl, steht;

der Rest „B“ für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 2 Heteroatome aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D“ für einen gesättigten oder teilweise ungesättigten 5- oder 6-gliedrigen Heterocyclus steht, der bis zu zwei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;

der Rest „M“ für –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A“, „B“ und „D“ jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Pyridyl; (C_1-C_3)-Alkanoyl; (C_6-C_{10})-Arylcarbonyl; (C_5-C_6)-Heteroarylcarbonyl; (C_1-C_3)-Alkanoyloxymethyloxy; -C($NR^{27}R^{28}$)=NR^{29}; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-Alkyl; und Cyclopropyl, Cyclopentyl oder Cyclohexyl,

wobei (C_1-C_4)-Alkyl und Cyclopropyl, Cyclopentyl oder Cyclohexyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; -OH; -OCH_3; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ und -C($NR^{27}R^{28}$)=NR^{29},

wobei:

v entweder 0 oder 1, vorzugsweise 0, bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder aber Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeuten

und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden können, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-Alkanoyl oder Phenylcarbonyl bedeuten,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_6)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze, Hydrate und Prodrugs,

ausgenommen jedoch Verbindungen der allgemeinen Formel (I), bei denen der Rest R^1 ein unsubstituierter 2-Thiophenrest ist und gleichzeitig der Rest R^2 einen ein- oder mehrfach substituierten Phenylrest darstellt und gleichzeitig die Reste R^3, R^4, R^5, R^6, R^7 und R^8 jeweils Wasserstoff bedeuten.

Insbesondere bevorzugt sind hierbei Verbindungen der allgemeinen Formel (I),

worin

R^1 für 2-Thiophen, steht, das gegebenenfalls in der 5-Position substituiert sein kann durch einen Rest aus der Gruppe Chlor, Brom, Methyl oder Trifluormethyl,

R^2 für eine der folgenden Gruppen steht:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

wobei:
der Rest „A" für Phenyl oder Naphthyl, insbesondere für Phenyl, steht;
der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 2 Heteroatome aus der Reihe S, N, NO (N-Oxid) und O enthält;
der Rest „D" für einen gesättigten oder teilweise ungesättigten 5- oder 6-gliedrigen Heterocyclus steht, der ein Stickstoffatom und gegebenenfalls ein weiteres Heteroatom und/oder Hetero-Kettenglied aus der Reihe S, SO, SO_2 und O; oder bis zu zwei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2 und O enthält;
der Rest „M" für –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- oder für eine kovalente Bindung steht;

wobei
die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus

der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Pyridyl; (C_1-C_3)-Alkanoyl; (C_6-C_{10})-Arylcarbonyl; (C_5-C_6)-Heteroarylcarbonyl; (C_1-C_3)-Alkanoyloxymethyloxy; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-Alkyl; und Cyclopropyl, Cyclopentyl oder Cyclohexyl,

wobei (C_1-C_4)-Alkyl und Cyclopropyl, Cyclopentyl oder Cyclohexyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; -OH; -OCH_3; -$NR^{28}R^{29}$; -$CO(NH)_v(NR^{27}R^{28})$ und -$C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1, vorzugsweise 0, bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder aber Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeuten

und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden können, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-Alkanoyl oder Phenylcarbonyl bedeuten,

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sind und für Wasserstoff oder für (C_1-C_4)-Alkyl stehen

und deren pharmazeutisch verträglichen Salze, Hydrate und Prodrugs,

ausgenommen jedoch Verbindungen der allgemeinen Formel (I), bei denen der Rest R^1 ein unsubstituierter 2-Thiophenrest ist und gleichzeitig der Rest R^2 einen ein- oder mehrfach substituierten Phenylrest darstellt und gleichzeitig die Reste R^3, R^4, R^5, R^6, R^7 und R^8 jeweils Wasserstoff bedeuten.

Ganz besonders bevorzugt sind hierbei Verbindungen der allgemeinen Formel (I),

worin

R^1 für 2-Thiophen, steht, das in der 5-Position substituiert ist durch einen Rest aus der Gruppe Chlor, Brom, Methyl oder Trifluormethyl,

R^2 für D-A- steht:

wobei:
der Rest „A“ für Phenylen steht;
der Rest „D“ für einen gesättigten 5- oder 6-gliedrigen Heterocyclus steht,
der über ein Stickstoffatom mit „A“ verknüpft ist,
der in direkter Nachbarschaft zum verknüpfenden Stickstoffatom eine Carbonylgruppe besitzt und
in dem ein Ring-Kohlenstoffglied durch ein Heteroatom aus der Reihe S, N und O ersetzt sein kann;

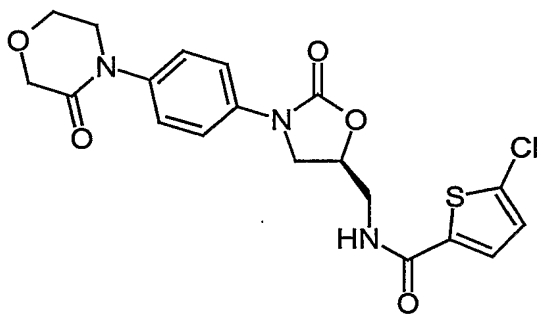
wobei

die zuvor definierten Gruppe „A" in der meta-Position bezüglich der Verknüpfung zum Oxazolidinon gegebenenfalls ein- oder zweifach substituiert sein kann mit einem Rest aus der Gruppe von Fluor, Chlor, Nitro, Amino, Trifluormethyl, Methyl oder Cyano,

R^3, R^4, R^5, R^6, R^7 und R^8 für Wasserstoff stehen

und deren pharmazeutisch verträglichen Salze, Hydrate und Prodrugs.

Ebenfalls ganz besonders bevorzugt ist hierbei die Verbindung mit der folgenden Formel



und ihre pharmazeutisch verträglichen Salze, Hydrate und Prodrugs.

Insbesondere kann in den Verbindungen der obigen allgemeinen Formel (I) der Rest

R^1 für gegebenenfalls benzokondensiertes Thiophen (Thienyl) stehen, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch einen Rest aus der Gruppe von Halogen; Cyano; Nitro; (C_1-C_8)-Alkyl, das gegebenenfalls seinerseits ein- oder mehrfach durch Halogen substituiert sein kann; (C_3-C_7)-Cycloalkyl; (C_1-C_8)-Alkoxy; Imidazolinyl; -C(=NH)NH_2; Carbamoyl; und Mono- und Di-(C_1-C_4)-alkyl-aminocarbonyl.

Vorzugsweise kann in den Verbindungen der allgemeinen Formel (I) der Rest

R^1 für Thiophen (Thienyl), insbesondere 2-Thiophen, stehen, das gegebenenfalls ein- oder mehrfach substituiert sein kann durch Halogen, vorzugsweise Chlor oder Brom, oder (C_1-C_8)-Alkyl, vorzugsweise Methyl, wobei der (C_1-C_8)-Alkylrest, vorzugsweise der Methylrest, gegebenenfalls seinerseits ein- oder mehrfach durch Halogen, vorzugsweise Fluor, substituiert sein kann.

In den Verbindungen der allgemeinen Formel (I) können die Reste

R^3, R^4, R^5, R^6, R^7 und R^8 gleich oder verschieden sein und insbesondere für Wasserstoff oder für (C_1-C_6)-Alkyl, vorzugsweise für Wasserstoff oder für (C_1-C_4)-Alkyl, ganz besonders bevorzugt für Wasserstoff, stehen.

Der Rest R^2, d.h. der organische Rest, kann insbesondere ausgewählt sein aus den im folgenden aufgeführten Substituentengruppen:

In den Verbindungen der allgemeinen Formel (I) kann der Rest

R^2 insbesondere für eine Gruppe der folgenden Formel stehen:

$$Y\text{-}X'\text{-}(CH_2)_p\text{-}X\text{-}(CO)_n\text{-}(CH_2)_{o_1}\text{-}(CR^9R^{10})_m\text{-}(CH_2)_{o_2}\text{-}$$

wobei:

m eine ganze Zahl zwischen 0 und 6, vorzugsweise zwischen 1 und 3, bedeutet,

n entweder 0 oder 1 bedeutet,

p eine ganze Zahl zwischen 0 und 3, vorzugsweise entweder 0 oder 1, bedeutet,

o_1 eine ganze Zahl 0 oder 1 bedeutet,

o_2 eine ganze Zahl 0 oder 1 bedeutet,

R^9 und R^{10} gleich oder verschieden sind und für Wasserstoff; (C_1-C_4)-Alkyl, vorzugsweise Methyl; (C_1-C_4)-Alkoxy, vorzugsweise Methoxy; (C_3-C_7)-Cycloalkyl; Hydroxy oder Fluor stehen,

X und X' gleich oder verschieden sind und für O; N-R^{11} oder eine kovalente Bindung stehen,

wobei R^{11} für H; (C_1-C_4)-Alkyl, vorzugsweise Methyl, oder (C_3-C_7)-Cycloalkyl steht,

Y für einen 3- bis 7-gliedrigen gesättigten oder teilweise ungesättigten cyclischen Kohlenwasserstoffrest steht, der gegebenenfalls 1 bis 3 gleiche oder verschiedene Heteroatome und/oder Hetero-Kettenglieder aus der Gruppe von N, O, S, SO und SO_2 enthält,

wobei:
dieser Rest Y gegebenenfalls substituiert sein kann durch einen 5- oder 6-gliedrigen aromatischen oder einen 3- bis 7-gliedrigen gesättigten oder teilweise ungesättigten cyclischen Kohlenwasserstoffrest, der gegebenenfalls bis zu 3 gleiche oder verschiedene Heteroatome aus der Gruppe von N, O und S enthält und

wobei dieser gegebenenfalls seinerseits substituiert sein kann durch einen Rest aus der Gruppe von Cyano; Hydroxy; Halogen; (C_1-C_4)-Alkyl; $-C(=NR^{12})NR^{13}R^{13'}$; und $-NR^{14}R^{15}$,

wobei:

R^{12} Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeutet;

R^{13} und $R^{13'}$ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeuten

und/oder

R^{13} und $R^{13'}$ gemeinsam mit dem N-Atom, an das sie gebunden sind, einen 5- bis 7-gliedrigen Heterocyclus bilden, der gegebenenfalls bis zu 2 weitere Heteroatomen aus der Reihe N, O und/oder S enthalten kann;

R^{14} und R^{15} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl oder (C_1-C_5)-Alkanoyl bedeuten;

und/oder

dieser Rest Y darüber hinaus gegebenenfalls substituiert sein kann durch einen Rest aus der Gruppe von Oxo; Cyano; Thiono; Halogen; $-OR^{16}$; $=NR^{16}$; $-NR^{16}R^{17}$; $-C(=NR^{18})NR^{19}R^{19'}$ und (C_1-C_4)-Alkyl,

worin (C_1-C_4)-Alkyl gegebenenfalls seinerseits substituiert sein kann durch einen Rest aus der Gruppe von Hydroxy; Cyano; $-NR^{16}R^{17}$ und $-C(=NR^{18})NR^{19}R^{19'}$,

wobei:

R^{16} und R^{17} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl oder (C_1-C_3)-Alkanoyl bedeuten;

R^{18} Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeutet;

R^{19} und $R^{19'}$ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeuten
und/oder
R^{19} und $R^{19'}$ gemeinsam mit dem N-Atom, an das sie gebunden sind, einen 5- bis 7-gliedrigen Heterocyclus bilden, der gegebenenfalls bis zu 2 weitere Heteroatomen aus der Reihe N, O und/oder S enthalten kann.

Besonders bevorzugt sind Verbindungen der allgemeinen Formel (I), bei denen der Rest

R^2 für eine Gruppe der folgenden Formel steht:

$$Y\text{-}X'\text{-}(CH_2)_p\text{-}X\text{-}(CO)_n\text{-}(CH_2)_{o_1}\text{-}(CR^9R^{10})_m\text{-}(CH_2)_{o_2}\text{-}$$

wobei

m eine ganze Zahl zwischen 0 und 3 bedeutet,

n eine ganze Zahl 0 oder 1 bedeutet,

p eine ganze Zahl 0 oder 1 bedeutet,

o_1 eine ganze Zahl 0 oder 1 bedeutet,

o_2 eine ganze Zahl 0 oder 1 bedeutet,

R^9 und R^{10} gleich oder verschieden sind und für Wasserstoff; Methyl; Methoxy; Hydroxy oder Fluor stehen,

X und X' gleich oder verschieden sind und für O; N-R^{11} oder eine kovalente Bindung stehen,

wobei R^{11} für H oder Methyl steht,

Y für einen 5- bis 7-gliedrigen gesättigten cyclischen Kohlenwasserstoffrest steht, der gegebenenfalls 1 oder 2 gleiche oder verschiedene Heteroatome und/oder Hetero-Kettenglieder aus der Gruppe von N, O, S, SO und SO_2 enthält, insbesondere Cyclohexyl, Piperazinyl, Morpholinyl, Thiomorpholinyl, Diazepinyl, Pyrrolidinyl und Piperidinyl,

wobei:

dieser Rest Y gegebenenfalls substituiert sein kann durch einen 5- oder 6-gliedrigen aromatischen oder einen 5- bis 7-gliedrigen gesättigten oder teilweise ungesättigten cyclischen Kohlenwasserstoffrest, der gegebenenfalls bis zu 2 gleiche oder verschiedene Heteroatome aus der Gruppe von N, O und S enthält und

wobei dieser gegebenenfalls seinerseits substituiert sein kann durch einen Rest aus der Gruppe von Cyano; Hydroxy; Fluor; Chlor; (C_1-C_4)-Alkyl; -C(=NR^{12})$NR^{13}R^{13'}$; und -$NR^{14}R^{15}$,

wobei:

R^{12} Wasserstoff, Methyl, Ethyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeutet;

R^{13} und $R^{13'}$ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, Methyl, Ethyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeuten
und/oder

R^{13} und $R^{13'}$ gemeinsam mit dem N-Atom, an das sie gebunden sind, einen 5- bis 7-gliedrigen Heterocyclus bilden, der gegebenenfalls bis zu 2 weitere Heteroatomen aus der Reihe N, O und/oder S enthalten kann, insbesondere Piperidinyl, Piperazinyl, Morpholinyl und Thiomorpholinyl;

R^{14} und R^{15} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, Methyl, Ethyl, Cyclopropyl, Cyclopentyl oder Cyclohexyl oder aber Acetyl bedeuten;

und/oder

dieser Rest Y darüber hinaus gegebenenfalls substituiert sein kann durch einen Rest aus der Gruppe von Oxo; Cyano; Thiono; Fluor; Chlor; -OH; $-OCH_3$; $=NR^{16}$; $-NH_2$; $-N(CH_3)_2$; $-C(=NR^{18})NR^{19}R^{19'}$ und Methyl,

worin Methyl gegebenenfalls seinerseits substituiert sein kann durch einen Rest aus der Gruppe von Hydroxy; Cyano; $-NR^{16}R^{17}$ und $-C(=NR^{18})NR^{19}R^{19'}$,

wobei:

R^{16} und R^{17} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, Methyl, (C_3-C_7)-Cycloalkyl oder Acetyl bedeuten;

R^{18} Wasserstoff, Methyl oder (C_3-C_7)-Cycloalkyl bedeutet;

R^{19} und $R^{19'}$ gleich oder verschieden sind und unabhängig voneinander Wasserstoff, Methyl oder (C_3-C_7)-Cycloalkyl bedeuten
und/oder

R^{19} und $R^{19'}$ gemeinsam mit dem N-Atom, an das sie gebunden sind, einen 5- bis 7-gliedrigen Heterocyclus bilden, der gegebenenfalls bis zu 2 weitere Heteroatomen aus der Reihe N, O und/oder S enthalten kann, insbesondere Piperidinyl, Piperazinyl, Morpholinyl und Thiomorpholinyl.

Ebenso kann in den Verbindungen der allgemeinen Formel (I) der Rest

R^2 für eine Gruppe der folgenden Formel stehen:

$$Z\text{-}(CO)_t\text{-}(CR^{20}R^{21})_s\text{-}$$

wobei:

s eine ganze Zahl zwischen 1 und 6 bedeutet,

t entweder 0 oder 1 bedeutet,

R^{20} und R^{21} gleich oder verschieden sind und für Wasserstoff, (C_1-C_4)-Alkyl, (C_1-C_4)-Alkoxy, (C_3-C_7)-Cycloalkyl, Hydroxy oder Fluor stehen,

Z für einen Rest steht, der ausgewählt ist aus der Gruppe von Cyano; $-C(NR^{22}R^{23})=NR^{24}$; $-CO(NH)_uNR^{22}R^{23}$; und $-NR^{25}R^{26}$,

wobei:

u entweder 0 oder 1, vorzugsweise 0, bedeutet und

R^{22}, R^{23} und R^{24} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl, vorzugsweise Wasserstoff oder Methyl, bedeuten
und/oder

R^{22} und R^{23} gemeinsam mit dem N-Atom, an das sie gebunden sind, einen 5- bis 7-gliedrigen Heterocyclus bilden, der gegebenenfalls bis zu 2 weitere Heteroatome und/oder Hetero-Kettenglieder aus der Reihe N, O, S, SO und/oder SO_2 enthalten kann;

R^{25} und R^{26} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl, vorzugsweise Wasserstoff, Methyl oder Ethyl, bedeuten, wobei (C_1-C_4)-Alkyl und (C_3-C_7)-Cycloalkyl ihrerseits gegebenenfalls durch Hydroxy oder (C_1-C_6)-Alkoxy substituiert sein können.

Des weiteren kann in den Verbindungen der allgemeinen Formel (I) der Rest

R^2 für eine der folgenden Gruppen stehen:

A-,
A-M-,
D-M-A-,
B-M-A-,
B-,
B-M-,
B-M-B-,
D-M-B-,

wobei:

der Rest „A" für (C_6-C_{14})-Aryl, vorzugsweise für (C_6-C_{10})-Aryl, insbesondere für Phenyl oder Naphthyl, ganz besonders bevorzugt für Phenyl, steht;
der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 3 Heteroatomen und/oder Hetero-Kettenglieder, insbesondere bis zu 2 Heteroatomen und/oder Hetero-Kettenglieder, aus der Reihe S, N, NO (N-Oxid) und O enthält;
der Rest „D" für einen gesättigten oder teilweise ungesättigten 4- bis 7-gliedrigen Heterocyclus steht, der bis zu drei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;
der Rest „M" für –NH-, -CH_2-, -CH_2CH_2-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO-, -COO-, -OOC-, -S- oder für eine kovalente Bindung steht;

wobei
die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Nitro; Carbamoyl; Pyridyl; (C_1-C_6)-Alkanoyl; (C_3-C_7)-Cycloalkanoyl; (C_6-C_{14})-Arylcarbonyl; (C_5-C_{10})-Heteroarylcarbonyl; (C_1-C_6)-Alkanoyloxymethyloxy; -$COOR^{27}$; -SO_2R^{27};

$-C(NR^{27}R^{28})=NR^{29}$; $-CONR^{28}R^{29}$; $-SO_2NR^{28}R^{29}$; $-OR^{30}$; $-NR^{30}R^{31}$, (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl,

wobei (C_1-C_6)-Alkyl und (C_3-C_7)-Cycloalkyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe von Cyano; $-OR^{27}$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ und $-C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1 bedeutet und

R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder (C_3-C_7)-Cycloalkyl bedeuten
und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu drei, vorzugsweise bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, (C_3-C_7)-Cycloalkyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_4)-Alkanoyl, (C_6-C_{14})-Arylcarbonyl, (C_5-C_{10})-Heteroarylcarbonyl, (C_1-C_4)-Alkylaminocarbonyl oder $-CH_2C(NR^{27}R^{28})=NR^{29}$ bedeuten.

Bevorzugt sind ebenso Verbindungen der allgemeinen Formel (I), bei denen der Rest

R^2 für eine der folgenden Gruppen steht:

A-,

A-M-,

D-M-A-,

B-M-A-,

B-,

B-M-,

B-M-B-,

D-M-B-,

wobei:

der Rest „A" für Phenyl oder Naphthyl, insbesondere für Phenyl, steht;

der Rest „B" für einen 5- oder 6-gliedrigen aromatischen Heterocyclus steht, der bis zu 2 Heteroatomen aus der Reihe S, N, NO (N-Oxid) und O enthält;

der Rest „D" für einen gesättigten oder teilweise ungesättigten 5- oder 6-gliedrigen Heterocyclus steht, der bis zu zwei Heteroatome und/oder Hetero-Kettenglieder aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und O enthält;

der Rest „M" für –NH-, -O-, -NH-CH_2-, -CH_2-NH-, -OCH_2-, -CH_2O-, -CONH-, -NHCO- oder für eine kovalente Bindung steht;

wobei

die zuvor definierten Gruppen „A", „B" und „D" jeweils gegebenenfalls ein- oder mehrfach substituiert sein können mit einem Rest aus der Gruppe von Halogen; Trifluormethyl; Oxo; Cyano; Pyridyl; (C_1-C_3)-Alkanoyl; (C_6-C_{10})-Arylcarbonyl; (C_5-C_6)-Heteroarylcarbonyl; (C_1-C_3)-Alkanoyloxymethyloxy; -$C(NR^{27}R^{28})$=NR^{29}; -$CONR^{28}R^{29}$; -$SO_2NR^{28}R^{29}$; -OH; -$NR^{30}R^{31}$; (C_1-C_4)-Alkyl; und Cyclopropyl, Cyclopentyl oder Cyclohexyl,

wobei (C_1-C_4)-Alkyl und Cyclopropyl, Cyclopentyl oder Cyclohexyl ihrerseits gegebenenfalls substituiert sein können durch einen Rest aus der Gruppe

von Cyano; -OH; $-OCH_3$; $-NR^{28}R^{29}$; $-CO(NH)_v(NR^{27}R^{28})$ und $-C(NR^{27}R^{28})=NR^{29}$,

wobei:

v entweder 0 oder 1, vorzugsweise 0, bedeutet und

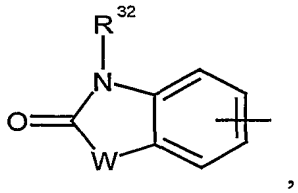
R^{27}, R^{28} und R^{29} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl oder aber Cyclopropyl, Cyclopentyl oder Cyclohexyl bedeuten
und/oder

R^{27} und R^{28} bzw. R^{27} und R^{29} zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen gesättigten oder teilweise ungesättigten 5- bis 7-gliedrigen Heterocyclus mit bis zu zwei gleichen oder unterschiedlichen Heteroatomen aus der Gruppe von N, O und S bilden können, und

R^{30} und R^{31} gleich oder verschieden sind und unabhängig voneinander Wasserstoff, (C_1-C_4)-Alkyl, Cyclopropyl, Cyclopentyl, Cyclohexyl, (C_1-C_4)-Alkylsulfonyl, (C_1-C_4)-Hydroxyalkyl, (C_1-C_4)-Aminoalkyl, Di-(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl, (C_1-C_3)-Alkanoyl oder Phenylcarbonyl bedeuten.

Ebenso kann in den Verbindungen der allgemeinen Formel (I) der Rest

R^2 für eine Gruppe der folgenden Formel stehen:



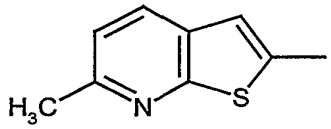
wobei

R^{32} für Wasserstoff oder (C_1-C_4)-Alkyl, vorzugsweise für Wasserstoff oder Methyl, und

W für S, NH oder O, vorzugsweise für S, steht.

Darüber hinaus kann in den Verbindungen der allgemeinen Formel (I) der Rest

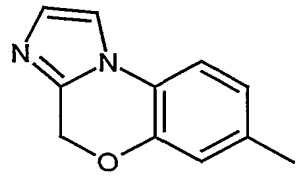
R^2 eine Gruppe der folgenden Formel



sein.

Schließlich kann in den Verbindungen der allgemeinen Formel (I) der Rest

R^2 eine Gruppe der folgenden Formel



sein.

Bislang sind Oxazolidinone im wesentlichen nur als Antibiotika, vereinzelt auch als MAO-Hemmer und Fibrinogen-Antagonisten beschrieben (Übersicht: Riedl, B.,

Endermann, R., Exp. Opin. Ther. Patents **1999**, *9* (5), 625), wobei für die antibakterielle Wirkung eine kleine 5-[Acyl-aminomethyl]-gruppe (bevorzugt 5-[Acetyl-aminomethyl]) essentiell zu sein scheint.

Substituierte Aryl- und Heteroarylphenyloxazolidinone, bei denen an das N-Atom des Oxazolidinonrings ein ein- oder mehrfach substituierte Phenylrest gebunden sein kann und die in der 5-Position des Oxazolidinonrings einen unsubstituierten N-Methyl-2-thiophencarboxamid-Rest aufweisen können, sowie ihre Verwendung als antibakteriell wirkende Substanzen sind bekannt aus den U.S.-Patentschriften US-A-5 929 248, US-A-5 801 246, US-A-5 756 732, US-A-5 654 435, US-A-5 654 428 und US-A-5 565 571.

Darüber hinaus sind benzamidinhaltige Oxazolidinone als synthetische Zwischenstufen bei der Synthese von Faktor Xa-Inhibitoren bzw. Fibrinogenantagonisten bekannt (WO-A-99/31092, EP-A-623615).

Die erfindungsgemäßen Verbindungen der allgemeinen Formel (I) können in Abhängigkeit von dem Substitutionsmuster in stereoisomeren Formen, die sich entweder wie Bild und Spiegelbild (Enantiomere) oder die sich nicht wie Bild und Spiegelbild (Diastereomere) verhalten, existieren. Die Erfindung betrifft sowohl die Enantiomeren oder Diastereomeren als auch deren jeweilige Mischungen. Die Racemformen lassen sich ebenso wie die Diastereomeren in bekannter Weise in die stereoisomer einheitlichen Bestandteile trennen.

Weiterhin können bestimmte Verbindungen der allgemeinen Formel (I) in tautomeren Formen vorliegen. Dies ist dem Fachmann bekannt, und derartige Verbindungen sind ebenfalls vom Umfang der Erfindung umfasst.

Physiologisch unbedenkliche, d.h. pharmazeutisch verträgliche Salze können Salze der erfindungsgemäßen Verbindungen mit anorganischen oder organischen Säuren sein. Bevorzugt werden Salze mit anorganischen Säuren wie beispielsweise

Chlorwasserstoffsäure, Bromwasserstoffsäure, Phosphorsäure oder Schwefelsäure, oder Salze mit organischen Carbon- oder Sulfonsäuren wie beispielsweise Essigsäure, Trifluoressigsäure, Propionsäure, Maleinsäure, Fumarsäure, Äpfelsäure, Zitronensäure, Weinsäure, Milchsäure, Benzoesäure, oder Methansulfonsäure, Ethansulfonsäure, Benzolsulfonsäure, Toluolsulfonsäure oder Naphthalindisulfonsäure.

Als pharmazeutisch verträgliche Salze können auch Salze mit üblichen Basen genannt werden, wie beispielsweise Alkalimetallsalze (z.B. Natrium- oder Kaliumsalze), Erdalkalisalze (z.B. Calcium- oder Magnesiumsalze) oder Ammoniumsalze, abgeleitet von Ammoniak oder organischen Aminen wie beispielsweise Diethylamin, Triethylamin, Ethyldiisopropylamin, Prokain, Dibenzylamin, N-Methylmorpholin, Dihydroabietylamin oder Methylpiperidin.

Als „Hydrate" werden erfindungsgemäß solche Formen der Verbindungen der obigen allgemeinen Formel (I) bezeichnet, welche in festem oder flüssigem Zustand durch Hydratation mit Wasser eine Molekül-Verbindung (Solvat) bilden. In den Hydraten sind die Wassermoleküle nebenvalent durch zwischenmolekulare Kräfte, insbesondere Wasserstoff-Brückenbindungen angelagert. Feste Hydrate enthalten Wasser als sogenanntes Kristall-Wasser in stöchiometrischen Verhältnissen, wobei die Wassermoleküle hinsichtlich ihres Bindungszustands nicht gleichwertig sein müssen. Beispiele für Hydrate sind Sesquihydrate, Monohydrate, Dihydrate oder Trihydrate. Gleichermaßen kommen auch die Hydrate von Salzen der erfindungsgemäßen Verbindungen in Betracht.

Als „Prodrugs" werden erfindungsgemäß solche Formen der Verbindungen der obigen allgemeinen Formel (I) bezeichnet, welche selbst biologisch aktiv oder inaktiv sein können, jedoch in die entsprechende biologisch aktive Form überführt werden können (beispielsweise metabolisch, solvolytisch oder auf andere Weise).

Halogen steht für Fluor, Chlor, Brom und Iod. Bevorzugt sind Chlor oder Fluor.

(C_1-C_8)-Alkyl steht für einen geradkettigen oder verzweigten Alkylrest mit 1 bis 8 Kohlenstoffatomen. Beispielsweise seien genannt: Methyl, Ethyl, n-Propyl, Isopropyl, n-Butyl, Isobutyl, tert.-Butyl, n-Pentyl und n-Hexyl. Aus dieser Definition leiten sich analog die entsprechenden Alkylgruppen mit weniger Kohlenstoffatomen wie z.B. (C_1-C_6)-Alkyl und (C_1-C_4)-Alkyl ab. Im allgemeinen gilt, dass (C_1-C_4)-Alkyl bevorzugt ist.

Aus dieser Definition leitet sich auch die Bedeutung des entsprechenden Bestandteils anderer komplexerer Substituenten ab wie z.B. bei Alkylsulfonyl, Hydroxyalkyl, Hydroxyalkylcarbonyl, Alkoxy-alkyl, Alkoxycarbonyl-alkyl, Alkanoylalkyl, Aminoalkyl oder Alkylaminoalkyl.

(C_3-C_7)-Cycloalkyl steht für einen cyclischen Alkylrest mit 3 bis 7 Kohlenstoffatomen. Beispielsweise seien genannt: Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl oder Cycloheptyl. Aus dieser Definition leiten sich analog die entsprechenden Cycloalkylgruppen mit weniger Kohlenstoffatomen wie z.B. (C_3-C_5)-Cycloalkyl ab. Bevorzugt sind Cyclopropyl, Cyclopentyl und Cyclohexyl.

Aus dieser Definition leitet sich auch die Bedeutung des entsprechenden Bestandteils anderer komplexerer Substituenten ab wie z.B. Cycloalkanoyl.

(C_2-C_6)-Alkenyl stehen im Rahmen der Erfindung für einen geradkettigen oder verzweigten Alkenylrest mit 2 bis 6 Kohlenstoffatomen. Bevorzugt ist ein geradkettiger oder verzweigter Alkenylrest mit 2 bis 4 Kohlenstoffatomen. Beispielsweise seien genannt: Vinyl, Allyl, Isopropenyl und n-But-2-en-1-yl.

(C_1-C_8)-Alkoxy steht für einen geradkettigen oder verzweigten Alkoxyrest mit 1 bis 8 Kohlenstoffatomen. Beispielsweise seien genannt: Methoxy, Ethoxy, n-Propoxy, Isopropoxy, n-Butoxy, Isobutoxy, tert.-Butoxy, n-Pentoxy, n-Hexoxy, n-Heptoxy und n-Oktoxy. Aus dieser Definition leiten sich analog die entsprechenden Alkoxy-

gruppen mit weniger Kohlenstoffatomen wie z.B. (C_1-C_6)-Alkoxy und (C_1-C_4)-Alkoxy ab. Im allgemeinen gilt, dass (C_1-C_4)-Alkoxy bevorzugt ist.

Aus dieser Definition leitet sich auch die Bedeutung des entsprechenden Bestandteils anderer komplexerer Substituenten ab wie z.B. Alkoxy-alkyl, Alkoxycarbonyl-alkyl und Alkoxycarbonyl.

Mono- oder Di-(C_1-C_4)-Alkylaminocarbonyl steht für eine Amino-Gruppe, die über eine Carbonylgruppe verknüpft ist und die einen geradkettigen oder verzweigten bzw. zwei gleiche oder verschiedene geradkettige oder verzweigte Alkylsubstituenten mit jeweils 1 bis 4 Kohlenstoffatomen aufweist. Beispielsweise seien genannt: Methylamino, Ethylamino, n-Propylamino, Isopropylamino, t-Butylamino, *N,N*-Dimethylamino, *N,N*-Diethylamino, *N*-Ethyl-*N*-methylamino, *N*-Methyl-*N*-n-propylamino, *N*-Isopropyl-*N*-n-propylamino und *N*-t-Butyl-*N*-methylamino.

(C_1-C_6)-Alkanoyl steht für einen geradkettigen oder verzweigten Alkylrest mit 1 bis 6 Kohlenstoffatomen, der in der 1-Position ein doppelt gebundenes Sauerstoffatom trägt und über die 1-Position verknüpft ist. Beispielsweise seien genannt: Formyl, Acetyl, Propionyl, n-Butyryl, i-Butyryl, Pivaloyl, n-Hexanoyl. Aus dieser Definition leiten sich analog die entsprechenden Alkanoylgruppen mit weniger Kohlenstoffatomen wie z.B. (C_1-C_5)-Alkanoyl, (C_1-C_4)-Alkanoyl und (C_1-C_3)-Alkanoyl ab. Im allgemeinen gilt, dass (C_1-C_3)-Alkanoyl bevorzugt ist.

Aus dieser Definition leitet sich auch die Bedeutung des entsprechenden Bestandteils anderer komplexerer Substituenten ab wie z.B. Cycloalkanoyl und Alkanoylalkyl.

(C_3-C_7)-Cycloalkanoyl steht für einen wie zuvor definierten Cycloalkylrest mit 3 bis 7 Kohlenstoffatomen, der über eine Carbonylgruppe verknüpft ist.

(C_1-C_6)-Alkanoyloxymethyloxy steht für einen geradkettigen oder verzweigten Alkanoyloxymethyloxy-Rest mit 1 bis 6 Kohlenstoffatomen. Beispielsweise seien

genannt: Acetoxymethyloxy, Propionoxymethyloxy, n-Butyroxymethyloxy, i-Butyroxymethyloxy, Pivaloyloxymethyloxy, n-Hexanoyloxymethyloxy. Aus dieser Definition leiten sich analog die entsprechenden Alkanoyloxymethyloxy-Gruppen mit weniger Kohlenstoffatomen wie z.B. (C_1-C_3)-Alkanoyloxymethyloxy ab. Im allgemeinen gilt, dass (C_1-C_3)-Alkanoyloxymethyloxy bevorzugt ist.

(C_6-C_{14})-Aryl steht für einen aromatischen Rest mit 6 bis 14 Kohlenstoffatomen. Beispielsweise seien genannt: Phenyl, Naphthyl, Phenanthrenyl und Anthracenyl. Aus dieser Definition leiten sich analog die entsprechenden Arylgruppen mit weniger Kohlenstoffatomen wie z.B. (C_6-C_{10})-Aryl ab. Im allgemeinen gilt, dass (C_6-C_{10})-Aryl bevorzugt ist.

Aus dieser Definition leitet sich auch die Bedeutung des entsprechenden Bestandteils anderer komplexerer Substituenten ab wie z.B. Arylcarbonyl.

(C_5-C_{10})-Heteroaryl oder ein 5- bis 10-gliedriger aromatischer Heterocyclus mit bis zu 3 Heteroatomen und/oder Heterokettengliedern aus der Reihe S, O, N und/oder NO (N-Oxid) steht für einen mono- oder bicyclischen Heteroaromaten, der über ein Ringkohlenstoffatom des Heteroaromaten, gegebenenfalls auch über ein Ringstickstoffatom des Heteroaromaten, verknüpft ist. Beispielsweise seien genannt: Pyridyl, Pyridyl-N-oxid, Pyrimidyl, Pyridazinyl, Pyrazinyl, Thienyl, Furyl, Pyrrolyl, Pyrazolyl, Imidazolyl, Thiazolyl, Oxazolyl oder Isoxazolyl, Indolizinyl, Indolyl, Benzo[b]thienyl, Benzo[b]furyl, Indazolyl, Chinolyl, Isochinolyl, Naphthyridinyl, Chinazolinyl. Aus dieser Definition leiten sich analog die entsprechenden Heterocyclen mit geringerer Ringgröße wie z.B. 5- oder 6-gliedrige aromatische Heterocyclen ab. Im allgemeinen gilt, dass 5- oder 6-gliedrige aromatische Heterocyclen wie z.B. Pyridyl, Pyridyl-N-oxid, Pyrimidyl, Pyridazinyl, Furyl und Thienyl bevorzugt sind.

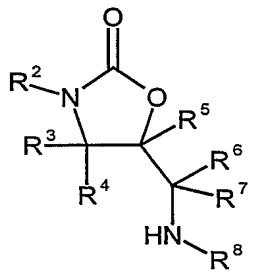
Aus dieser Definition leitet sich auch die Bedeutung des entsprechenden Bestandteils anderer komplexerer Substituenten ab wie z.B. (C_5-C_{10})-Heteroarylcarbonyl.

Ein 3- bis 9-gliedriger gesättigter oder teilweise ungesättigter, mono- oder bicyclischer, gegebenenfalls benzokondensierter Heterocyclus mit bis zu 3 Heteroatomen und/oder Heterokettengliedern aus der Reihe S, SO, SO_2, N, NO (N-Oxid) und/oder O steht für einen Heterocyclus, der eine oder mehrere Doppelbindungen enthalten kann, der mono- oder bicyclisch sein kann, bei dem an zwei benachbarte Ringkohlenstoffatomen ein Benzolring ankondensiert sein kann und der über ein Ringkohlenstoffatom oder ein Ringstickstoffatom verknüpft ist. Beispielsweise seien genannt: Tetrahydrofuryl, Pyrrolidinyl, Pyrrolinyl, Piperidinyl, 1,2-Dihydropyridinyl, 1,4-Dihydropyridinyl, Piperazinyl, Morpholinyl, Morpholinyl-N-oxid, Thiomorpholinyl, Azepinyl, 1,4-Diazepinyl und Cyclohexyl. Bevorzugt sind Piperidinyl, Morpholinyl und Pyrrolidinyl.

Aus dieser Definition leiten sich analog die entsprechenden Cyclen mit geringerer Ringgröße wie z.B. 5- bis 7-gliedrige Cyclen ab.

Gegenstand der vorliegenden Erfindung ist auch ein Verfahren zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I), wobei man entweder gemäß einer Verfahrensalternative

[A] Verbindungen der allgemeinen Formel (II)

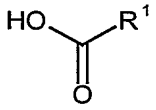


(II),

in welcher

die Reste R^2, R^3, R^4, R^5, R^6, R^7und R^8 die oben angegebenen Bedeutungen haben,

mit Carbonsäuren der allgemeinen Formel (III)



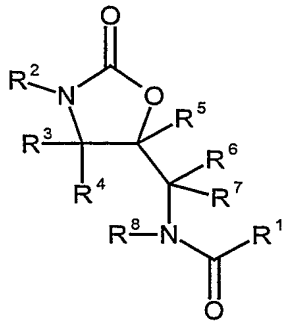
(III),

in welcher

der Rest R^1 die oben angegebene Bedeutung hat,

oder aber mit den entsprechenden Carbonsäurehalogeniden, vorzugsweise Carbonsäurechloriden, oder aber mit den entsprechenden symmetrischen oder gemischten Carbonsäureanhydriden der zuvor definierten Carbonsäuren der allgemeinen Formel (III)

in inerten Lösungsmitteln, gegebenenfalls in Gegenwart eines Aktivierungs- oder Kupplungsreagenzes und/oder einer Base, zu Verbindungen der allgemeinen Formel (I)



(I),

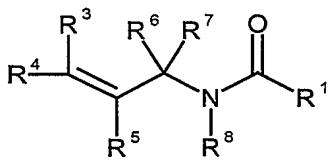
in welcher

die Reste R^1, R^2, R^3, R^4, R^5, R^6, R^7 und R^8 die oben angegebenen Bedeutungen haben,

umsetzt,

oder aber gemäß einer Verfahrensalternative

[B] Verbindungen der allgemeinen Formel (IV)

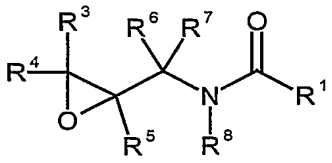


(IV),

in welcher

die Reste R^1, R^3, R^4, R^5, R^6, R^7 und R^8 die oben angegebenen Bedeutungen haben,

mit einem geeigneten selektiven Oxidationsmittel in einem inerten Lösungsmittel in das entsprechenden Epoxid der allgemeinen Formel (V)



(V),

in welcher

die Reste R^1, R^3, R^4, R^5, R^6, R^7 und R^8 die oben angegebenen Bedeutungen haben,

überführt,

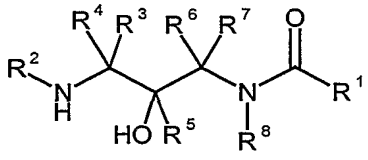
und durch Umsetzung in einem inerten Lösungsmittel gegebenenfalls in Gegenwart eines Katalysators mit einem Amin der allgemeinen Formel (VI)

$$R^2 - NH_2 \qquad (VI),$$

in welcher

der Rest R^2 die oben angegebene Bedeutung hat,

zunächst die Verbindungen der allgemeinen Formel (VII)



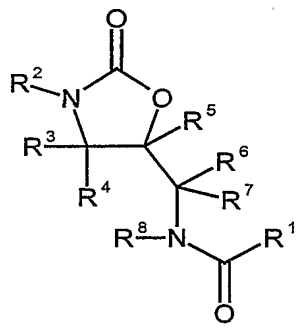
(VII),

in welcher

die Reste R^1, R^2, R^3, R^4, R^5, R^6, R^7 und R^8 die oben angegebenen Bedeutungen haben,

herstellt und

anschließend in inertem Lösungsmittel in Anwesenheit von Phosgen oder Phosgenäquivalenten wie z.B. Carbonyldiimidazol (CDI) zu den Verbindungen der allgemeinen Formel (I)



(I)

in welcher

die Reste R^1, R^2, R^3, R^4, R^5, R^6, R^7 und R^8 die oben angegebenen Bedeutungen haben,

cyclisiert,

wobei sich sowohl für die Verfahrensalternative [A] als auch für die Verfahrensalternative [B] für den Fall, dass R^2 einen 3- bis 7- gliedrigen gesättigten oder teilweise ungesättigten cyclischen Kohlenwasserstoffrest mit einem oder mehreren gleichen oder verschiedenen Heteroatomen aus der Gruppe von N und S enthält, eine Oxidation mit einem selektiven Oxidationsmittel zum entsprechenden Sulfon, Sulfoxid oder N-Oxid anschließen kann

und/oder

wobei sich sowohl für die Verfahrensalternative [A] als auch für die Verfahrensalternative [B] für den Fall, dass die auf diese Weise hergestellte Verbindung eine Cyanogruppe im Molekül aufweist, eine Amidinierung dieser Cyanogruppe mit den üblichen Methoden anschließen kann

und/oder

wobei sich sowohl für die Verfahrensalternative [A] als auch für die Verfahrensalternative [B] für den Fall, dass die auf diese Weise hergestellte Verbindung eine BOC-Aminoschutzgruppe im Molekül aufweist, eine Abspaltung dieser BOC-Aminoschutzgruppe mit den üblichen Methoden anschließen kann

und/oder

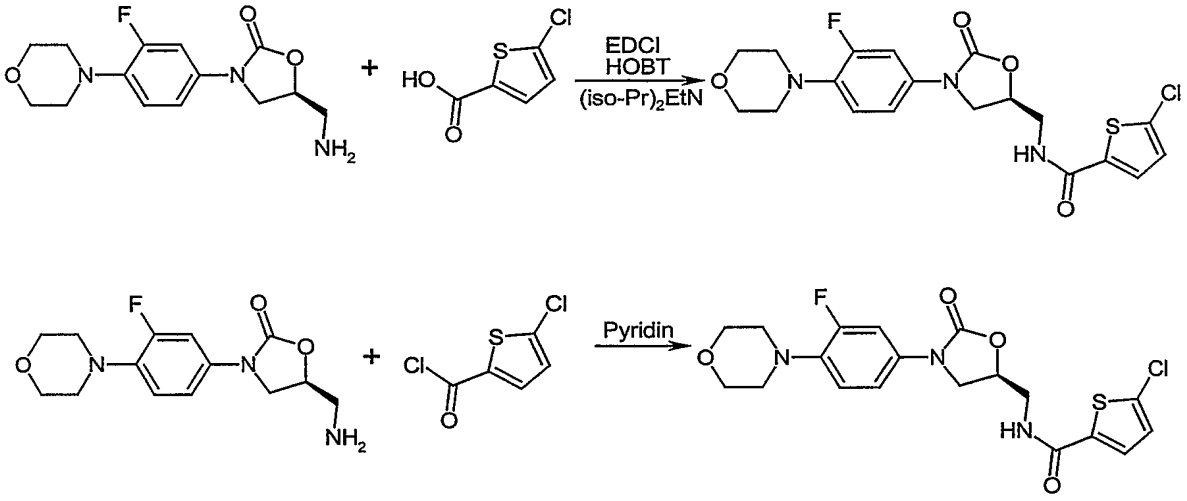
wobei sich sowohl für die Verfahrensalternative [A] als auch für die Verfahrensalternative [B] für den Fall, dass die auf diese Weise hergestellte Verbindung einen Anilin- oder Benzylaminrest im Molekül aufweist, eine Umsetzung dieser Aminogruppe mit verschiedenen Reagenzien wie Carbonsäuren, Carbonsäureanhydriden, Carbonsäurechloriden, Isocyanaten, Sulfonsäurechloriden oder Alkylhalogeniden zu den entsprechenden Derivaten anschließen kann

und/oder

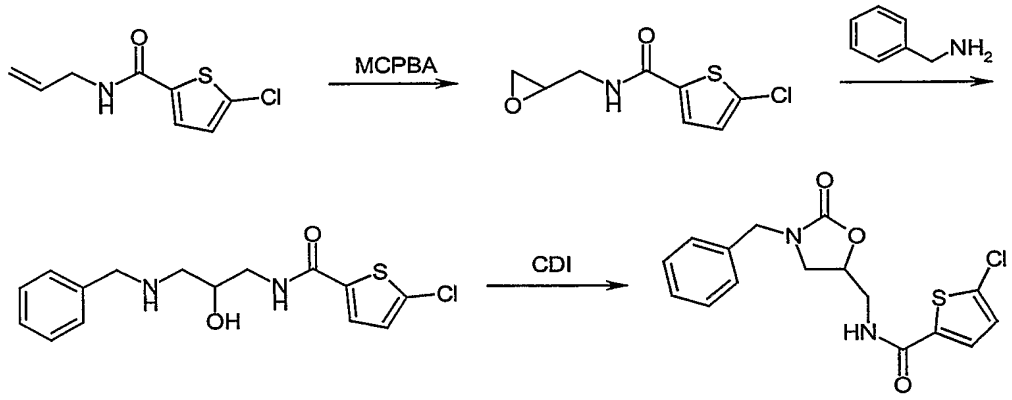
wobei sich sowohl für die Verfahrensalternative [A] als auch für die Verfahrensalternative [B] für den Fall, dass die auf diese Weise hergestellte Verbindung einen Phenylring im Molekül aufweist, eine Reaktion mit Chlorsulfonsäure und anschließende Umsetzung mit Aminen zu den entsprechenden Sulfonamiden anschließen kann.

Die erfindungsgemäßen Verfahren können durch folgende Formelschemata beispielhaft erläutert werden:

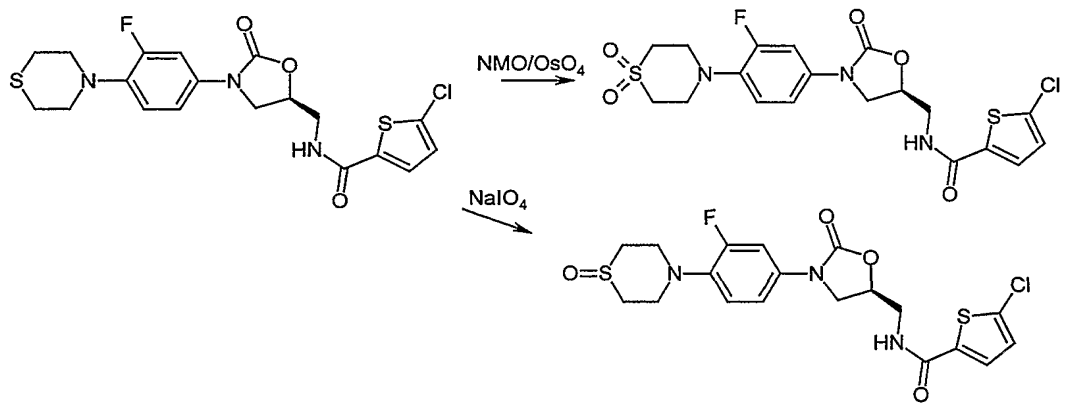
[A]



[B]



Der zuvor beschriebene, gegebenenfalls erfolgende Oxidationsschritt kann durch folgende Formelschemata beispielhaft erläutert werden:



Als Lösemittel für die zuvor beschriebenen Verfahren eignen sich hierbei organische Lösemittel, die unter den Reaktionsbedingungen inert sind. Hierzu gehören Halogenkohlenwasserstoffe wie Dichlormethan, Trichlormethan, Tetrachlormethan, 1,2-Dichlorethan, Trichlorethan, Tetrachlorethan, 1,2-Dichlorethylen oder Trichlorethylen, Ether wie Diethylether, Dioxan, Tetrahydrofuran, Glykoldimethylether oder Diethylenglykoldimethylether, Alkohole wie Methanol, Ethanol, n-Propanol, iso-Propanol, n-Butanol oder tert.-Butanol, Kohlenwasserstoffe wie Benzol, Xylol, Toluol, Hexan oder Cyclohexan, Dimethylformamid, Dimethylsulfoxid, Acetonitril, Pyridin, Hexamethylphosphorsäuretriamid oder Wasser.

Ebenso ist es möglich, Lösemittelgemische der zuvor genannten Lösemittel einzusetzen.

Als Aktivierungs- oder Kupplungsreagenzien für die zuvor beschriebenen Verfahren eignen hierbei die hierfür üblicherweise verwendeten Reagenzien, beispielsweise *N'*-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimid • HCl, *N,N'*-Dicyclohexylcarbodiimid, 1-Hydroxy-1H-benzotriazol • H_2O und dergleichen.

Als Basen eignen sich die üblichen anorganischen oder organischen Basen. Hierzu gehören bevorzugt Alkalihydroxide wie beispielsweise Natrium- oder Kaliumhydroxid oder Alkalicarbonate wie Natrium- oder Kaliumcarbonat oder Natrium- oder Kaliummethanolat oder Natrium- oder Kaliumethanolat oder Kalium-tert.-butylat

oder Amide wie Natriumamid, Lithium-bis-(trimethylsilyl)amid oder Lithiumdiisopropylamid oder Amine wie Triethylamin, Diisopropylethylamin, Diisopropylamin, 4-*N,N*-Dimethylaminopyridin oder Pyridin.

Die Base kann hierbei in einer Menge von 1 bis 5 Mol, bevorzugt von 1 bis 2 Mol, bezogen auf 1 Mol der Verbindungen der allgemeinen Formel (II), eingesetzt werden.

Die Reaktionen erfolgen im allgemeinen in einem Temperaturbereich von –78°C bis zur Rückflusstemperatur, bevorzugt im Bereich von 0°C bis Rückflusstemperatur.

Die Umsetzungen können bei normalem, erhöhtem oder erniedrigtem Druck durchgeführt werden (z.B. im Bereich von 0,5 bis 5 bar). Im allgemeinen arbeitet man bei Normaldruck.

Als geeignete selektive Oxidationsmittel sowohl für die Herstellung der Epoxide als auch für die gegebenenfalls durchgeführte Oxidation zum Sulfon, Sulfoxid oder N-Oxid kommen beispielsweise m-Chlorperbenzoesäure (MCPBA), Natriummetaperiodat, N-Methylmorpholin-N-oxid (NMO), Monoperoxyphthalsäure oder Osmiumtetroxid in Betracht.

Hinsichtlich der Herstellung der Epoxide werden die hierfür üblichen Herstellungsbedingungen angewandt.

Hinsichtlich der näheren Verfahrensbedingungen für die gegebenenfalls durchgeführte Oxidation zum Sulfon, Sulfoxid oder N-Oxid kann verwiesen werden auf die folgende Literatur: M. R. Barbachyn et al., J. Med. Chem. **1996**, *39*, 680 sowie WO-A-97/10223.

Des weiteren wird auf die im experimentellen Teil aufgeführten Beispiele 14 bis 16 verwiesen.

Die gegebenenfalls durchgeführte Amidinierung erfolgt unter üblichen Bedingungen. Für weitere Einzelheiten kann auf die Beispiele 31 bis 35 und 140 bis 147 verwiesen werden.

Die Verbindungen der allgemeinen Formeln (II), (III), (IV) und (VI) sind dem Fachmann an sich bekannt oder nach üblichen Methoden herstellbar. Für Oxazolidinone, insbesondere die benötigten 5-(Aminomethyl)-2-oxooxazolidine, vgl. WO-A-98/01446; WO-A-93/23384; WO-A-97/03072; J. A. Tucker et al., J. Med. Chem. **1998**, *41*, 3727; S. J. Brickner et al., J. Med. Chem. **1996**, *39*, 673; W. A. Gregory et al., J. Med. Chem. **1989**, *32*, 1673.

Die erfindungsgemäßen Verbindungen der allgemeinen Formel (I) zeigen ein nicht vorhersehbares, wertvolles pharmakologisches Wirkspektrum und sind daher insbesondere zur Prophylaxe und/oder Behandlung von Erkrankungen geeignet.

Die erfindungsgemäßen Verbindungen der allgemeinen Formel (I) - einschließlich auch der per Disclaimer vom Stoffschutz ausgeschlossenen Verbindungen - wirken insbesondere als Antikoagulantien und können daher bevorzugt eingesetzt werden in Arzneimitteln zur Prophylaxe und/oder Behandlung von thromboembolischen Erkrankungen. Zu den „thromboembolischen Erkrankungen“ im Sinne der vorliegenden Erfindung zählen insbesondere schwerwiegende Erkrankungen wie Herzinfarkt, Angina Pectoris (eingeschlossen instabile Angina), Reokklusionen und Restenosen nach einer Angioplastie oder aortokoronarem Bypass, Hirnschlag, transitorische ischämische Attacken, periphere arterielle Verschlusskrankheiten, Lungenembolien oder tiefe venöse Thrombosen.

Darüber hinaus sind die erfindungsgemäßen Verbindungen der allgemeinen Formel (I) - einschließlich auch der per Disclaimer vom Stoffschutz ausgeschlossenen Verbindungen - gleichermaßen zur Behandlung der disseminierten intravasalen Gerinnung (DIC) geeignet.