USE OF AN INDAZOLEMETHOXYALKANOIC ACID TO PREPARE A PHARMACEUTICAL COMPOSITION

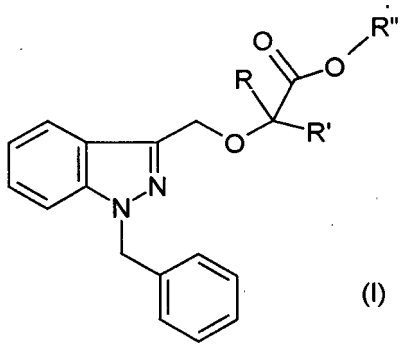
Description

FIELD OF THE INVENTION

[0001] The present invention relates to the use of an indazolemethoxy-alkanoic acid according to formula I of claim 1 to prepare a pharmaceutical composition for reducing the blood triglyceride, cholesterol and/or glucose levels.

PRIOR ART

[0002] Document EP-B1-0 382 276 describes a compound of formula (I):



(I)

in which

R and R', which may be the same or different, are H or C_{1-5} alkyl, and
R" is H or C_{1-4} alkyl,

optionally, when R" is H, in the form of a salt thereof with a pharmaceutically acceptable organic or mineral base.

[0003] The abovementioned document also points out that the compound of formula (I) has analgesic activity.

[0004] For the sake of brevity, the abovementioned compound of formula (I) in which R, R' and R" have the above-mentioned meanings will be referred to hereinbelow as the compound of formula (I). Thus, in the course of the present description, the expression "compound of formula (I) in which R and R', which may be the same or different, are H or C_{1-5} alkyl, and R" is H or C_{1-4} alkyl, optionally, when R" is H, in the form of a salt thereof with a pharmaceutically acceptable organic or mineral base" and the expression "compound of formula (I)" are equivalent.

[0005] Document EP-B1-0 510 748 describes the use of a compound of formula (I) to prepare a drug that is active in the treatment of autoimmune diseases.

[0006] In addition, document EP-B1-0 858 337 describes a pharmaceutical composition comprising a compound of formula (I) in which R = R' = CH_3 and R" = H, and an immunosuppressant.

[0007] Finally, document EP-B1-1 005 332 reports that the compound of formula (I) reduces the production of the protein MCP-1. More particularly, the said document describes the use of a compound of formula (I) to prepare a pharmaceutical composition for treating a disease chosen from the group comprising atherosclerosis, interstitial lung diseases, and post-operative complications in heart surgery, transplants, organ or tissue replacements, or prosthesis implants.

SUMMARY OF THE INVENTION

[0008] It has now been found, surprisingly, that the compound of formula (I) reduces the blood triglyceride, cholesterol and glucose levels.

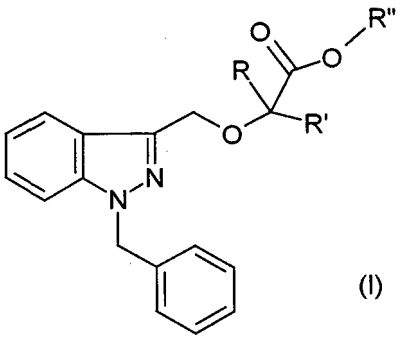
[0009] The reason for this activity has not yet been entirely elucidated, but, without thereby wishing to limit the present invention, it is thought that this could be related to the capacity of the compound of formula (I) to inhibit the expression of IL-12.

[0010] As is known, IL-12 is a cytokine produced by monocytes, macrophages, neutrophils, dendritic cells and antibody-producing B cells, and also by keratinocytes and a number of tumoral cell lines (epidermoid carcinoma).

[0011] IL-12 modulates the activation of the "natural killer" (NK) cells and T cells, and the induction of interferon-gamma (IFN-γ), which is a cytokine that participates in regulating the immune response.

DETAILED DESCRIPTION OF THE INVENTION

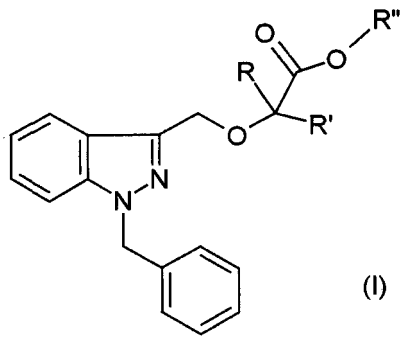
[0012] In a first aspect, the present invention relates to the use of a compound of formula (I):



(I)

in which
R and R', which may be the same or different, are H or C_{1-5} alkyl, and
R" is H or C_{1-4} alkyl,
optionally, when R" is H, in the form of a salt thereof with a pharmaceutically acceptable organic or mineral base,
to prepare a pharmaceutical composition for reducing the blood triglyceride, cholesterol and glucose levels.

[0013] In a second aspect, the present invention relates to a pharmaceutical composition for the treatment of hypertriglyceridemia, hypercholesterolemia, hyperglycaemia comprising an effective dose of a compound of formula (I):



(I)

in which
R and R', which may be the same or different, are H or C_{1-5} alkyl, and
R" is H or C_{1-4} alkyl, optionally, when R" is H, in the form of a salt thereof with a pharmaceutically acceptable organic or mineral base.

[0014] A preferred compound of formula (I) is that in which R" is H and R = R' = CH_3. This compound is known as "bindarit".

[0015] By virtue of their capacity to normalize the blood triglyceride, cholesterol and glucose levels, the pharmaceutical compositions according to the present invention will be useful for treating hypertriglyceridemia, hypercholesterolemia or hyperglycaemia.

[0016] Obesity may be considered as a chronic pathological condition resulting from complex interactions between cultural, psychological and genetic factors. In the last thirty years, there has been a great increase in interest in the pharmacological control of obesity and related health problems, moreover on account of the social costs associated with this condition. Much evidence has demonstrated that being overweight or obese substantially increases the risk of death caused by various conditions including diabetes, hypertension, dyslipidaemia, coronary cardiopathies, congestive heart insufficiency, myocardial infection, and even certain of forms of cancer. In addition, a higher body weight is also associated with increased mortality in general.

[0017] Obesity and insulin resistance share a complex relationship that leads to the development of various types of metabolic disorder, including type-2 diabetes. The adipocytes accumulate triglycerides and release free fatty acids, which are cholesterol precursors, that can play an important role in the development and progression of diabetes and its associated disorders.

[0018] High levels of circulating lipids may be the consequence of various pathological conditions or, in turn, may be the cause of specific diseases.

[0019] Disorders commonly related with high levels of lipids (hyperlipidaemia) include cardiovascular diseases or conditions including coronary disorders, hypertension, thrombosis, ischaemic events, for instance infarction, strokes and organ insufficiency.

[0020] In addition, for certain individuals, the simultaneous presence of the symptoms described above, which include hypertension, hyperlipidaemia and obesity, may indicate a particular predisposition to diabetes and to cardiovascular disorders, a condition currently indicated as metabolic syndrome.

[0021] In recent decades, the prevalence of obesity and related disorders has increased exponentially, reaching epidemic proportions in the United States and Europe. Recent estimates suggest that, despite the continued efforts made by the public health organizations, the health problems of obese and overweight individuals will continue to increase.

[0022] Consequently, the targeted and effective treatment of obesity is a primary objective of the pharmaceutical industry.

[0023] Preferably, the pharmaceutical compositions of the present invention are prepared in suitable dosage forms comprising an effective dose of at least one compound of formula (I) and at least one pharmaceutically acceptable inert ingredient.

[0024] Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; medicated plasters, pastes, creams and ointments for transdermal administration; suppositories for rectal administration and sterile solutions for administration via the injection or aerosol route.

[0025] Other examples of suitable dosage forms are those with sustained release and based on liposomes for administration via either the oral or injection route.

[0026] The dosage forms may also contain other conventional ingredients, for instance preserving agents, stabilizers, surfactants, buffers, osmotic pressure-regulating salts, emulsifiers, sweeteners, colorants, flavourings and the like.

[0027] In addition, when required for particular therapies, the pharmaceutical composition according to the present invention may also contain other pharmacologically active ingredients whose simultaneous administration is useful.

[0028] The amount of compound of formula (I) in the pharmaceutical composition according to the present invention may vary within a wide range as a function of known factors, for instance the type of disease to be treated, the severity of the disease, the body weight of the patient, the dosage form, the selected route of administration, the number of daily administrations and the efficacy of the selected compound of formula (I). However, a person skilled in the art may determine the optimum amount in a simple and routine manner.

[0029] Typically, the amount of compound of formula (I) in the pharmaceutical composition according to the present invention will be such that it provides a level of administration of between 0.0001 and 100 mg/kg/day. Preferably, the level of administration is between 0.05 and 50 mg/kg/day and even more preferably between 0.1 and 10 mg/kg/day.

[0030] The dosage forms of the pharmaceutical composition according to the present invention may be prepared according to techniques that are well known to pharmaceutical chemists, including mixing, granulation, compression, dissolution, sterilization and the like.

[0031] The activity of the compound of formula (I) was evaluated *in vitro* in human monocytes by means of gene expression analysis techniques using "GeneChip" and *in vivo* in Zucker rats, an experimental model of type-2 diabetes characterized by glucose intolerance and insulin resistance accompanied by hyperglycaemia and hyperlipidaemia.

[0032] As is known to those skilled in the art, the abovementioned experimental models are predictive of activity in man.

Test 1

Analysis of the gene expression in human monocytes (GeneChip Technology)

[0033] The capacity of bindarit to inhibit the expression of IL-12 by human monocytes stimulated with lipopolysaccharide (LPS) was evaluated.

[0034] Human monocytes were used, which were isolated from healthy donors by centrifugation on a Ficoll gradient and purified by two successive centrifugation steps, followed by a step of isolation by means of an immunomagnetic system of negative cell separation (MACS, Miltenyi Biotech), using specific antibodies.

[0035] The cells were stimulated with LPS (100 ng/ml) for 4 hours in the presence or absence of bindarit (300 μM). The product was tested in the form of the sodium salt obtained by salification with equimolar sodium hydroxide and subsequent dilution in the medium used. The total RNA was extracted from cells using TRizol (Invitrogen Life Technologies) according to manufacturer's instructions, reverse-transcribed and prepared by GeneChip hybridization.

[0036] As shown by the results obtained given in Figure 1, bindarit is capable of significantly inhibiting the expression of LPS-induced IL-12 in human monocytes, reducing the levels of specific mRNA by about 100-fold.

[0037] Similar results were obtained using bindarit in acid form dissolved in DMSO.

Test 2

Effect of bindarit on circulating levels of triglycerides, cholesterol and glucose in Zucker rats

[0038] The activity of bindarit was tested in an experimental model in rats.
[0039] The study was performed on rats 5 weeks old on arrival, of the Zucker strain homozygous for the "fa" allele (fa/fa), insulin-resistant, hyperinsulinaemic and obese, and on rats of the same age of the heterozygous Zucker control strain (fa/+), phenotypically normal, insulin-sensitive and slim.
[0040] At six weeks old, the obese Zucker rats were divided into two groups, one of which was fed with a standard rodent diet, and the other with a standard rodent diet supplemented with 0.5% bindarit.
[0041] The slim Zucker rats of the same age were used as controls and fed with a standard rodent diet.
[0042] Blood samples were taken from the animals periodically (at 6, 16, 28 and 40 weeks old) for enzymatic measurement of the circulating levels of triglycerides, cholesterol and glucose.
[0043] The results are illustrated in Figures 2, 3 and 4.
[0044] Figures 2 and 3 show that the administration of bindarit induces a significant reduction in the circulating levels of triglycerides and cholesterol.
[0045] Figure 4 shows that, as a consequence of the glucose intolerance and the insulin resistance characteristic of the strain of rats used, the obese animals show an increase in glycaemia. The treatment with bindarit induces a significant reduction in the glycaemia.
[0046] The diabetic syndrome characteristic of the obese Zucker rats shows many similarities with human type-2 diabetes and is also accompanied by appreciable hyperlipidaemia.
[0047] The following examples of pharmaceutical compositions are given to illustrate the invention in greater detail without, however, limiting it.

Example 1

Tablets

[0048]

Each tablet contains:

a)	Active substance:	
	Bindarit	300 mg
b)	Excipients:	
	Microcrystalline cellulose	66 mg
	Corn starch	50 mg
	Sodium starch glycolate	19 mg
	Povidone	18 mg
	Colloidal silicon dioxide	14.5 mg
	Magnesium stearate	4.5 mg

Example 2

[0049] Liposomes for administration via the oral and/or injection route

a)	Active substance:	
	Bindarit	4 mg/ml
b)	Liposome composition (w/w%):	
	Phosphatidylcholine	94
	Lysophosphatidylcholine	3
	N-Acylethanolamine	1
	Phosphatidylethanolamine	0.1
	Triglycerides	1
	Free fatty acids	0.75
	DL-α-tocopherol	0.15

Example 3

Granulate

[0050]

Formula A

Each sachet contains:

a)	Active substance:	
	Bindarit	300 mg
b)	Excipients:	
	Trometamol	230 mg
	Maltitol	1850 mg
	Mannitol	1600 mg
	K-Acesulfame	30 mg
	Sucralose	30 mg
	Flavourings	100 mg

Formula B

Each sachet contains:

a)	Active substance:	
	Bindarit sodium salt	309.25 mg
	(equal to 300 mg of free acid)	
b)	Excipients:	
	Potassium bicarbonate	300 mg
	Sucrose	2500 mg
	Flavourings	70 mg
	K-Acesulfame	50 mg
	Aspartame	20 mg

Example 4

Oral drops

[0051]

a)	Active substance:		
	Bindarit		20 g
b)	Excipients:		
	Potassium hydroxide		7 g
	Sucrose		20 g
	Sucralose		0.5 g
	Polysorbate-20		0.2 g
	Methyl p-hydroxybenzoate		0.018 g
	Propyl p-hydroxybenzoate		0.011 g
	Disodium edetate		0.01 g
	Glycerol		15 g
	Flavourings		6 g
	Purified water	qs	100 ml

Example 5

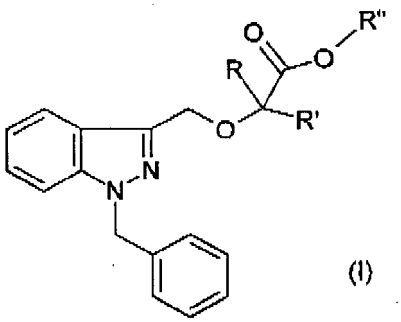
Injectable solutions

[0052]

	Each vial contains:		
a)	Active substance:		
	Bindarit		0.3 g
b)	Excipients:		
	Trometamol		0.24 g
	Poloxamer		0.01 g
	Sodium edetate		0.001 g
	Water for injection	qs	10 ml

Claims

1. Use of a compound of formula (I):



(I)

in which

R and R', which may be the same or different, are H or C_{1-5} alkyl, and
R" is H or C_{1-4} alkyl,
optionally, when R" is H, in the form of a salt thereof with a pharmaceutically acceptable organic or mineral base, in the manufacture of a pharmaceutical composition for treating hypertriglyceridemia, hypercholesterolemia, or hyperglycaemia.

2. Use of a compound of formula (I) according to Claim 1, in which R" is H and R = R' = CH_3.

3. Use of a compound of formula (I) according to Claim 1, in which R" is Na and R = R' = CH_3.