

6-aryl-9-glycosylpurines and use thereof

Field of Art

- 5 The invention relates to 6-(benzylamino/furfurylamino)-9- β -D-arabinofuranosylpurine or - β -D-2'-deoxyribofuranosylpurine derivatives which slow down the aging of animal and human cells and which show UV photoprotective properties.

Background Art

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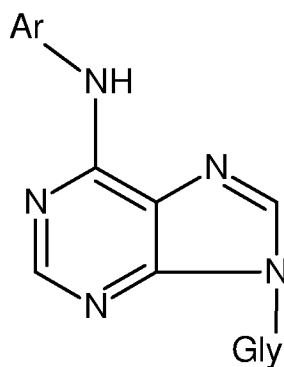
Substituted adenine derivatives are known as phytohormones. The range of their properties is rather broad, especially known is their anti-tumor and pro-apoptotic activity, i.e., activities relating to inhibition of tumor cell growth. Several glycosylated derivatives were prepared, in particular ribosylated derivatives. An arabinosylated derivative prepared so far was 6-benzylamino-9-arabinosylpurine which was published as a compound participating in inhibition of replication of tobacco mosaic virus in extirpated leaves *Nicotiana glutinosa* (Barai et al. Vestsi Akademii Nauk Belarusi 1: 18-22, 1992). 6-chloropurine arabinoside was prepared from 6-chloropurine riboside and its antiviral activity was explored (Maruyama et al. Chem. Pharm. Bull. 44: 2331-2334, 1996). Several methylated derivatives of 6-(benzylamino)-9- β -D-arabinofuranosylpurine were prepared for antiviral activity testing, and their activity in killing *Vaccinia* virus and *Herpes simplex* virus was tested. No effect was observed for benzylamino derivative, neither for 2-methylbenzyl, 3-methylbenzyl, 2,3-dimethylbenzyl, 2,6-dimethylbenzyl, 3,4-dimethylbenzyl derivatives. A low activity against *Vaccinia* virus, strain IHD, was observed for 2,4-dimethylbenzyl and 2,5-dimethylbenzyl substituents (Masakatsu et al. Chem. Pharm. Bull. 25: 2482-2489, 1977). Some N6-substituted derivatives of adenine arabinoside were prepared as selective inhibitors of varicella-zoster virus, the substituents were 6-methylamino, 6-dimethylamino-, 6-ethylamino-, 6-N-ethylmethylamino-, NN-diethylamino-, 6-n-propylamino-, 6-isopropylamino-, 6-n-hexylamino-, 6-cyclohexylamino-, 6-anilino (Koszalka et al. Antimicrob. Agents Chemother. 35: 1437-1443, 1991).

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The object of the present invention are glycosylated derivatives of adenine with antisenescence and photoprotective properties which show extremely low or no toxicity and high activity in aging, cell division and differentiation processes and photoprotection.

5 Disclosure of the Invention

Object of the invention is use of 6-aryl-9-glycosylpurines of general formula I



I

and pharmaceutically acceptable salts thereof with alkali metals, ammonia, amines, or addition salts with acids, wherein

Gly represents β -D-arabinofuranosyl or β -D-2'-deoxyribofuranosyl,

15 **Ar** represents benzyl or furfuryl, each of which can be unsubstituted or substituted by one or more, preferably one to three, substituents selected from the group comprising hydroxyl, alkyl, halogen, alkoxy, amino, mercapto, carboxyl, cyano, amido, sulfo, sulfamido, acyl, acylamino, acyloxy, alkylamino, dialkylamino, alkylmercapto, trifluoromethyl, trifluoromethoxy,

20 for regulation, in particular inhibition, of aging in animals, in particular mammals, for cosmetic purposes, and/or for UV photoprotection of animals, in particular mammals, for cosmetic purposes.

The invention further encompasses the 6-aryl-9-glycosylpurines of general formula I for
25 use in a method of regulation, in particular inhibition, of aging in animals, in particular

mammals, for therapeutic purposes, and/or for UV photoprotection of animals, in particular mammals, for therapeutic purposes.

Another object of the invention is a method for regulating aging and/or UV photodamage of microorganisms, and animal cells *in vitro*, in which at least one compound of general formula I is applied to the plant or cells or microorganisms.

If not stated otherwise, then:

alkyl represents a linear or branched C1-C6, preferably C1-C4, alkyl chain,

10 acyl represents an acyl group having 2 to 6 carbon atoms,

halogen represents a halogen atom selected from the group consisting of fluorine, bromine, chlorine and iodine atom,

sulfo represents $-\text{SO}_3\text{R}_c$, wherein R_c represents hydrogen atom, linear or branched alkyl, alkenyl or alkynyl group containing 1 to 6 carbon atoms,

15 sulfoamido represents $-\text{NHSO}_3\text{R}_d$, wherein R_d represents hydrogen atom, linear or branched alkyl group containing 1 to 6 carbon atoms.

Particularly preferred compounds of the invention are the compounds of formula I selected from the group consisting of: 6-furfurylamino-9- β -D-arabinofuranosylpurine, 6-(3-methylfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-methylfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(5-methylfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-fluorofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-fluorofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(5-fluorofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-chlorofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-chlorofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(5-chlorofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-bromofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-bromofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(5-bromofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-hydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-hydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(5-hydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(5-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2-aminofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-aminofurfurylamino)-9- β -D-

arabinofuranosylpurine, 6-(4-aminofurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3,5-dihydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,4-dihydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,5-dihydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,6-dihydroxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3,4-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3,4-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3,5-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,3-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,4-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,5-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2,6-dimethoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-3-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-4-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-5-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-6-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-hydroxy-2-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-hydroxy-4-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-hydroxy-5-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(3-hydroxy-6-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-hydroxy-2-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-hydroxy-3-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-hydroxy-5-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(4-hydroxy-6-methoxyfurfurylamino)-9- β -D-arabinofuranosylpurine, 6-(2-fluorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(3-fluorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(4-fluorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-bromobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(3-bromobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(4-bromobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(3-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(4-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-chlorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(3-chlorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(4-chlorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-

- methoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-methoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-methoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-hydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-hydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-hydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-hexylbenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-fluoro-6-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-chloro-2,6-difluorobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-(trifluoromethylthio)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-chloro-3,6-difluorobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-(trifluoromethylthio)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-fluoro-5-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-chloro-4-fluorobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-(trifluoromethoxy)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-chloro-3-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-fluoro-3-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,5-bis(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-(trifluoromethoxy)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-(trifluoromethoxy)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-aminobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-aminobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-aminobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-diethylaminobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,5-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,4-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,5-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,6-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3,5-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,3-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,4-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,5-

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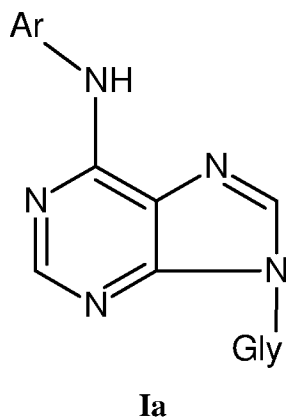
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deoxyribofuranosylpurine, 6-(3,5-dihydroxyfurfurylamino)-9- β -D-2'-
25 deoxyribofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9- β -D-2'-
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- deoxyribofuranosylpurine, 6-(2,4-dimethoxyfurfurylamino)-9-β-D-2'-
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 deoxyribofuranosylpurine, 6-(3-bromobenzylamino)-9-β-D-2'-deoxyribofuranosylpurine,
 20 6-(4-bromobenzylamino)-9-β-D-2'-deoxyribofuranosylpurine, 6-(2-iodobenzylamino)-9-β-
 D-2'-deoxyribofuranosylpurine, 6-(3-iodobenzylamino)-9-β-D-2'-
 deoxyribofuranosylpurine, 6-(4-iodobenzylamino)-9-β-D-2'-deoxyribofuranosylpurine, 6-
 (2-chlorobenzylamino)-9-β-D-2'-deoxyribofuranosylpurine, 6-(2-chlorobenzylamino)-9-β-
 D-2'-deoxyribofuranosylpurine, 6-(3-chlorobenzylamino)-9-β-D-2'-
 25 deoxyribofuranosylpurine, 6-(4-chlorobenzylamino)-9-β-D-2'-deoxyribofuranosylpurine,
 6-(2-aminobenzylamino)-9-β-D-2'-deoxyribofuranosylpurine, 6-(3-aminobenzylamino)-9-
 β-D-2'-deoxyribofuranosylpurine, 6-(4-aminobenzylamino)-9-β-D-2'-
 deoxyribofuranosylpurine, 6-(2-methoxybenzylamino)-9-β-D-2'-deoxyribofuranosylpurine,
 6-(3-methoxybenzylamino)-9-β-D-2'-deoxyribofuranosylpurine, 6-(4-
 30 methoxybenzylamino)-9-β-D-2'-deoxyribofuranosylpurine, 6-(2-hydroxybenzylamino)- 9-
 β-D-2'-deoxyribofuranosylpurine, 6-(3-hydroxybenzylamino)-9-β-D-2'-
 deoxyribofuranosylpurine, 6-(4-hydroxybenzylamino)-9-β-D-2'-deoxyribofuranosylpurine,

	6-(3,4-dihydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3,5-
	dihydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3,4-
	dihydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,4-
	dihydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,5-
5	dihydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,6-
	dihydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3,4-
	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3,4-
	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3,5-
	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,3-
10	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,4-
	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,5-
	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2,6-
	dimethoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2-hydroxy-3-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2-hydroxy-4-
15	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2-hydroxy-5-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(2-hydroxy-6-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3-hydroxy-2-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3-hydroxy-4-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3-hydroxy-5-
20	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(3-hydroxy-6-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(4-hydroxy-2-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(4-hydroxy-3-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(4-hydroxy-5-
	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine,	6-(4-hydroxy-6-
25	methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine.	

Object of the invention are further compositions for inhibiting aging and/or for UV photoprotection of mammals, or for inhibiting aging and/or for UV photoprotection of mammalian cells, such as keratinocytes and fibroblasts, containing at least one 6-aryl-9-glycosidpurine of general formula I.

Object of the invention are also 6-aryl-9-glycosidpurines of general formula **Ia**



and pharmaceutically acceptable salts thereof with alkali metals, ammonia, amines, or
5 addition salts with acids, wherein

Gly represents β -D-arabinofuranosyl or β -D-2'-deoxyribofuranosyl,

Ar represents benzyl or furfuryl, each of which is substituted by one or more, preferably
one to three, substituents selected from the group comprising hydroxyl, halogen, alkoxy,
amino, mercapto, carboxyl, cyano, amido, sulfo, sulfamido, acyl, acylamino, acyloxy,
10 alkylamino, dialkylamino, alkylmercapto, trifluoromethyl, trifluoromethoxy, or **Ar** is
unsubstituted furfuryl,

whereas, if **Gly** is β -D-arabinofuranosyl, **Ar** is not methyl-substituted benzyl.

The invention further encompasses cosmetic and/or tissue compositions containing as an
15 active ingredient at least one compound of general formula **Ia**. Tissue compositions are
especially suitable for use in biotechnologies.

Compositions

20 Suitable administration for cosmetic application is local, topical. The cosmetic composition
typically contains from 0.1 to 95 wt. % of the active ingredient, whereas single-dose forms
contain preferably 10 to 90 wt. % of the active ingredient and administration forms which
are not single-dose preferably comprise 1 wt. % to 10wt. % of the active ingredient. The
application forms include, e.g., ointments, creams, pastes, foams, tinctures, lipsticks, drops,
25 sprays, dispersions and the like. The compositions are prepared in a known manner, for
example by means of conventional mixing, dissolving or lyophilizing processes.

Solutions of the active ingredients, suspensions or dispersions, especially isotonic aqueous solutions, dispersions and suspensions, can be prepared before use, for example in the case of lyophilised compositions which comprise the active substance alone or together with a carrier, for example mannitol.

- 5 Suspensions in oil comprise, as the oily component, vegetable, synthetic or semi-synthetic oils. Oils which may be mentioned are, in particular, liquid fatty acid esters which contain, as the acid component, a long-chain fatty acid having 8-22, in particular 12-22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidonic acid, behenic acid or corresponding
- 10 unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasidic acid or linoleic acid, if appropriate with the addition of antioxidants, for example vitamin E, β -carotene or 3,5-di-*tert*-butyl-4-hydroxytoluene. The alcohol component of these fatty acid esters has not more than 6 carbon atoms and is mono- or polyhydric, for example mono-, di- or trihydric alcohol, for example methanol, ethanol, propanol, butanol, or pentanol, or isomers thereof,
- 15 but in particular glycol and glycerol. Fatty acid esters are, for example: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate from Gattefoscé, Paris), "Labrafil M 1944 CS" (unsaturated polyglycolated glycerides prepared by an alcoholysis of apricot kernel oil and composed of glycerides and polyethylene glycol esters; from Gattefoscé, Paris), "Labrasol" (saturated polyglycolated
- 20 glycerides prepared by an alcoholysis of TCM and composed of glycerides and polyethylene glycol esters; from Gattefoscé, Paris) and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length C₈ to C₁₂ from Hüls AG, Germany), and in particular vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and, in particular, groundnut oil.
- 25 Ointments are oil-in-water emulsions which comprise not more than 70 %, preferably 20 to 50 % of water or aqueous phase. The fatty phase consists, in particular, of hydrocarbons, for example vaseline, paraffin oil or hard paraffins, which preferably comprise suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol, or wool wax alcohols, such as wool wax, to improve the water-binding capacity. Emulsifiers
- 30 are corresponding lipophilic substances, such as sorbitan fatty acid esters (Spans), for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, for

example, humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, or preservatives and odoriferous substances.

Fatty ointments are non-aqueous and are in particular hydrocarbon-based, e.g. paraffin, vaseline or paraffin oil, and natural or semi-synthetic lipids, such as hydrogenated coconut fatty acid triglycerides or hydrogenated oils, such as hydrogenated castor or groundnut oil, and partially fatty acid glycerol esters, e.g. glycerol mono- and distearate. They further contain, e.g., fatty alcohols, emulsifiers and additives mentioned above in connection with ointments which increase water binding.

Creams are oil-in-water emulsions containing more than 50 % of water. The oil bases used include fatty alcohols, e.g., isopropyl myristate, lanolin, bees wax or hydrocarbons, preferably vaseline (petrolatum) and paraffine oil. Emulsifiers are surface active compounds with predominantly hydrophilic characteristics, such as corresponding non-ionic emulsifiers, e.g., fatty acid polyalcohol esters or ethyleneoxy adducts thereof, e.g., polyglyceridic fatty acids or polyethylene sorbitan esters or acidic polyglyceridic fatty acid esters (Tween), polyoxyethylene fatty acid ethers or polyoxyethylene fatty acid esters; or corresponding ionic emulsifiers, such as alkali sulfate salts of fatty alcohols, such as sodium laurylsulfate, sodium cetylsulfate, or sodium stearylsulfate, which are typically used in the presence of fatty alcohols, e.g., cetyl stearyl alcohol or stearyl alcohol. The aqueous phase additives include agents preventing drying out of the creams, e.g., polyalcohols such as glycerol, sorbitol, propylene glycol and polyethylene glycol, and preservatives and fragrances.

Pastes are creams or ointments containing powdered secretion-absorbing components such as metal oxides, e.g., titanium oxides or zinc oxide, further talc or aluminium silicates for binding humidity or secretion.

Foams are applied from pressurized containers and include liquid oil-in-water emulsions in aerosol form, whereas the propellant gases include halogenated hydrocarbons such as chloro-fluoro-lower alkanes, e.g., dichlorofluoromethane and dichlorotetrafluoroethane, or preferably non-halogenated gaseous hydrocarbons, air, N₂O or carbon dioxide. The oily phases used are the same as for ointments and the additives mentioned for ointments are used.

Tinctures and solutions usually comprise an aqueous-ethanolic base, to which humectants for reducing evaporation, such as polyalcohols, for example glycerol, glycols and/or

polyethylene glycol, and re-oiling substances, such as fatty acid esters with lower polyethylene glycols, i.e. lipophilic substances soluble in the aqueous mixture to substitute the fatty substances removed from the skin with ethanol, and, if necessary, other excipients and additives, are admixed.

5

The invention is further illustrated by the following examples which should not be construed as further limiting.

Brief Description of Drawings

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Fig. 1: Growth curve for the compound 6-benzylamino-9- β -D-arabinofuranosylpurine (Example 15).

Fig. 2: Effect of 6-furfurylamino-9- β -D-arabinofuranosylpurine (2212) and 3-fluorobenzylamino-9- β -D-arabinofuranosylpurine (2213) on the retention of chlorophyll in extirpated wheat leaf segments (Example 18).

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Fig. 3. UVA-induced effects of test compounds on NHDF viability of 6(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine (Example 20).

Fig. 4. UVA-induced effect of chlorpromazine on NHDF viability (Example 20).

Fig. 5. Effect of test compounds on UVA-induced damage to NHDF. (A) 6(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine (Example 21).

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Fig. 6. Effect of test compounds on UVB-induced damage to NHDF. (A) 6(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine (Example 21).

Fig. 7. Venn diagrams of 3MeOBAPA-responsive genes as revealed in the short-term (6 h) and long-term (48 h) treatments (Example 22).

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Examples of carrying out the Invention

EXAMPLE 1: Synthesis of 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine

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9-(β -D-arabinofuranosyl) hypoxanthine (100 mg, 0.37 mmol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 196 mg, 0.44 mmol) and *N,N*-diisopropylethylamine (DIPEA, 97 μ l, 0.56 mmol) were mixed in

dimethylformamide (DMF, 1.86 ml). Subsequently, 3-methoxybenzylamine (56 μ l, 0.56 mmol) was added. 9-(β -D-arabinofuranosyl) hypoxanthine is commercially available (Jena Bioscience, N-1002) or can be prepared from 9-(β -D-arabinofuranosyl) adenine. Reaction mixture was mixed at laboratory temperature (25 °C) under argon overnight (16 hrs). After that period, reaction mixture was evaporated on vacuum rotary evaporator and one of the following procedures was used to obtain the crude product: First, the reaction mixture was purified by column liquid chromatography (mobile phase chloroform-methanol 19:1) or cold water was slowly added (15 ml) and the reaction mixture was vortexed: a yellowish substance started to occur after a few minutes. Reaction mixture was then placed into the fridge and left overnight. Arising product was filtrated and once recrystallized from isopropanol and twice from ethanol. Final product is a white crystalline solid. Both ways of isolation of the product described above gave 40 % yield, TLC (40% chlorform:metanol (90:10, v:v): one spot; HPLC purity > 98%. $[M+H^+]$ 388, 1H (DMSO- d_6 , 300 MHz) δ ppm: 3.65-3.66 (m, 2H), 3.70 (s, 3H), 3.78 (d, J = 3,7 Hz), 4.14 (s, 2H), 4.67 (bs, 2H), 5.09 (t, J = 5,3 Hz), 5.52 (d, J = 3,8 Hz), 5.61 (d, J = 4,5 Hz), 6.27 (d, J = 3,9 Hz), 6.77 (d, J = 7,1 Hz), 6.89 (s, 1H), 6.91 (s, 1H), 7.20 (t, J = 7,6 Hz), 8.19 (s, 1H), 8.21 (s, 1H), 8.34 (bs, 1H).

EXAMPLE 2: Synthesis of 6-(3-hydroxybenzylamino)-9- β -D-arabinofuranosylpurine

20

9-(β -D-arabinofuranosyl) hypoxanthine (100 mg, 0.37 mmol), BOP (196 mg, 0.44 mmol) and DIPEA (97 μ l, 0.56 mmol) were mixed in v DMF (1.86 ml). Subsequently, 3-hydroxybenzylamine (50 μ l, 0.50 mmol) was added. 9-(β -D-arabinofuranosyl) hypoxanthine is commercially available (Jena Bioscience, N-1002). Reaction mixture was mixed under argon atmosphere at laboratory temperature (25 °C) overnight (10 hrs). Reaction mixture was evaporated using vacuum rotary evaporator and purified by column liquid chromatography (mobile phase chloroform: methanol 19/1). Product is a white crystalline solid, yield 5%, TLC (chlorform:metanol (90:10, v:v): one spot; HPLC purity > 98%, $[M+H^+]$ 374, NMR: 1H (DMSO- d_6 , 300 MHz) δ ppm: 3.66 (s, 2H), 3.78 (s, 1H), 4.15 (s, 2H), 4.63 (bs 2H), 5.12 (s, 1H), 5.55 (s, 1H), 5.64 (s, 1H), 6.28 (s, 1H), 6.58 (d, J = 7,5 Hz), 6.73 (s, 1H), 6.76 (s, 1H), 7.07 (t, J = 7,5 Hz), 8.19 (s, 1H), 8.21 (s, 1H), 9.27 (bs, 1H).

EXAMPLE 3: Synthesis of 6-(3-fluorobenzylamino)-9- β -D-arabinofuranosylpurine

9-(β -D-arabinofuranosyl) hypoxantine (100 mg, 0.37 mmol), BOP (196 mg, 0.44 mmol) and
5 DIPEA (97 μ l, 0.56 mmol) were mixed together in DMF (1.86 ml) and subsequently, 3-
fluorobenzylamine (70 μ l, 0.76 mmol) was added. 9-(β -D-arabinofuranosyl) hypoxantine
was prepared from commercially available 9-(β -D-arabinofuranosyl)adenine. Reaction
mixture was mixed under argon at laboratory temperature of 25 °C for 24 h. Reaction
mixture was evaporated on vacuum rotary evaporator and cold water was added after small
10 portions of 15 ml. After several minutes of vortexing, yellowish substance started to occur.
Reaction mixture was then refridgerated for 10 hrs. A product was filtered off and once
recrystallized using isopropanol and twice using ethanol. Produkt is a white crystalline
solid, in both cases of isolation, the yield 70%, TLC (chlorform:metanol (90:10, v:v): one
spot; HPLC purity > 98%. [M+H⁺] 376, NMR: ¹H(DMSO-*d*₆, 300 MHz) δ ppm: 3.66 (s,
15 2H), 3.79 (s, 1H), 4.14 (s, 2H), 4.74 (bs, 2H), 5.09 (s, 1H), 5.50 (s, 1H), 5.60 (s, 1H), 6.29
(s, 1H), 7.17 (s, 4H), 8.22 (s, 2H), 8.37 (bs, 1H).

EXAMPLE 4: Synthesis of 6-(3-iodobenzylamino)-9- β -D-arabinofuranosylpurine

20 9-(β -D-arabinofuranosyl) hypoxantine (100 mg, 0.37 mmol), BOP (196 mg, 0.44 mmol)
were mixed together in DMF (2 ml) and subsequently, 3-iodbenzylamine (60 μ l) and
DIPEA (97 μ l) was added. 9-(β -D-arabinofuranosyl) hypoxantine was prepared from
commercially available 9-(β -D-arabinofuranosyl)adenine. Reaction mixture was mixed
under argon atmosphere in oil bath at the temperature of 60 °C for 24 h. Reaction mixture
25 was evaporated on vacuum rotary evaporator. Arising gel was absorbed to silicagel and
chromatography columns was used for sample purification using chloroform:methanol
mobile phase with the gradient 99:1 to 9:1. TLC (chlorform:metanol (90:10, v:v): one spot;
HPLC purity > 98%. [M+H⁺] 484, NMR: ¹H(DMSO-*d*₆, 300 MHz) δ ppm: ¹H(DMSO-*d*₆,
500 MHz) δ ppm: 3.6 (s,1H), 3.7 (s,1H), 3.76-3.81 (m,2H), 4.09-4.17 (m,2H), 4.64
30 (bs,1H), 5.23 (bs,1H), 5.66 (bs,2H), 6.24 (d, J=5 Hz, 1H), 7.09 (t, J=7,5 Hz, 1H), 7.34 (d,
J=7,5 Hz, 1H), 7.55 (d, J=8 Hz, 1H), 7.69 (s, 1H), 8.18 (s, 1H), 8.21 (s, 1H), 8.37 (bs, 1H)

EXAMPLE 5: Synthesis of 6-furfurylamino-9- β -D-arabinofuranosylpurine

6-chloropurine tetraacetylarabinopyranoside (100 mg, 0.242 mmol) dispersed in methanol (3 ml) was placed into microwave reactor CEM SP reaction vessel (10 ml). Subsequently, furfurylamine (26.8 μ l, 0.291 mmol) with triethylamine (151 μ l, 1.09 mmol) were added. Reaction conditions were adjusted as follows: dynamic method, it means: reaction time 3 hrs, temperature: 100 °C, pressure 100 psi and performance: 50 watt. Reaction mixture was evaporated using vacuum rotary evaporator and purified using column liquid chromatography (mobile phase: chloroform:methanol 9/1). The product is a white solid: kinetin arabinopyranoside, mixture of α and β anomers in ration 5/1. The anomers were separated from each other: yield: 30% of α anomer and 10% of β anomer. Starting compound 6-chloropurine tetraacetylarabinopyranoside was prepared as follows: 6-chloropurine (0.412 g, 2.66 mmol) was placed into a dry flask and a tetraacetylarabinose (0.771g 2.42 mmol) dissolved in dry acetonitrile was added through the septum by a needle (15ml). Subsequently, tin tetrachloride was slowly added by a needle (5.6 mmol 0.6 ml). Reaction mixture was mixed at laboratory temperature under argon overnight. After that period, a mixture was evaporated using vacuum evaporater and ethylacetate (25 ml) was added. Organic phase was extracted by sodium carbonate solution (30 ml) and water(2 x 30 ml) and after that dried over sodium sulphate and again evaporated using vacuum evaporator. A product was purified by column liquid chromatography, mobile dichlormethane-aceton 9/1. As the result after the evaporation of organic solvents, there occurred clear gel like residue and this residue was mixed with diethyl ether and changed into a white solid 6-chloropurine tetraacetylarabinopyranosid, a mixture of α and β anomers. Yield: 50 %, HPLC purity: 98%, $[M+H]^+$ 348, NMR: $^1H(DMSO-d_6, 300 MHz)$ δ ppm: 3.61-3.72 (m, 2H), 3.78 (d, $J = 3,9$ Hz), 4.14 (s, 2H), 4.69 (bs, 2H), 5.11 (t, $J = 5,4$ Hz), 5.54 (d, $J = 3,9$ Hz), 5.62 (d, $J = 4,8$ Hz), 6.22 (d, $J = 2,7$ Hz), 6.27 (d, $J = 4,2$ Hz), 6.36 (t, $J = 3,0$ Hz), 7.54 (s, 1H), 8.21 (s, 3H).

EXAMPLE 6: Synthesis of 6-(2-chlorobenzylamino)-9- β -D-arabinofuranosylpurine

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9-(β -D-arabinofuranosyl) hypoxantine (100 mg, 0.37 mmol), BOP (196 mg, 0.44 mmol) were mixed together in DMF (2 ml) and subsequently, 2-chlorobenzylamine (55 μ l) and

DIPEA (97 μ l) was added. Reaction mixture was mixed under argon atmosphere in oil bath at the temperature of 60 °C for 24 h. Reaction mixture was evaporated on vacuum rotary evaporator. MeOH with a drop of chloroform was added to distillation residue and the mixture was ultrasonised. The process formed arising of a white paste solid that was
 5 filtrated. The resulted white solid was re-crystallized from EtOH and left in refridgerator overnight. Result was a white solid. TLC (chlorform:metanol (90:10, v:v): one spot; HPLC purity > 98%. [M+H⁺] 392, NMR: ¹H(DMSO-*d*₆, 300 MHz) δ ppm: ¹H(DMSO-*d*₆, 500 MHz) δ ppm: 3.60-3.71 (m,2H), 3.77 (q,J=4 Hz,1H), 4.11-4.15 (m,2H), 4.69 (bs,2H), 5.14 (bs,1H), 5.57 (bs,2H), 6.25 (d,J=4,5 Hz,1H), 7.25-7.33 (m,3H), 7.36 (s,1H), 8.18 (s,1H),
 10 8.21 (s,1H), 8.40 (bs,1H).

EXAMPLE 7: The synthesis of 6-(2-aminobenzylamino)-9- β -D-arabinofuranosylpurine
 9-(β -D-arabinofuranosyl) hypoxantine (100 mg, 0.37 mmol),BOP (196 mg, 0.44 mmol) were mixed together in DMF (2 ml) and subsequently, 2-aminobenzylamine (55 μ l) and
 15 DIPEA (97 μ l) was added. Reaction mixture was mixed under argon atmosphere in oil bath at the temperature of 60 °C for 24 h. Reaction mixture was evaporated on vacuum rotary evaporator. The resulted distillation residue was re-crystallized from EtOH and left in refridgerator overnight. Result was a white solid that was filtrated off and dried. TLC (chlorform:metanol (90:10, v:v): one spot; HPLC purity > 98%, NMR: ¹H(DMSO-*d*₆, 300
 20 MHz) δ ppm: ¹H(DMSO-*d*₆, 500 MHz) δ ppm: 3.59-3.70(m,2H), 3.77(q,J=4Hz,1H), 4.11-4.15(m,2H), 4.51(bs,2H), 5.10(t,J=5.5Hz,1H), 5.20(s,2H), 5.52(d,J=4Hz,1H), 5.60(d,J=5Hz,1H), 6.26(d,J=4hz,1H), 6.46(t,J=7.5Hz,1H), 6.59(d,J=8Hz,1H), 6.91(t,J=7.5Hz,1H), 7.07(d,J=7.5Hz,1H), 8.19(s,3H)

25 Table 1: 6-substituted-9- β -D-arabinofuranosylpurines prepared by the method according to Examples 1-7, elemental analyses and ES-MS measurement results of these compouds

Substituent in position 6 (-NH-Ar)	Elemental analysis calculated/found			ES-MS [M+H ⁺]
	%C	%H	%N	
furfurylamino	51.9/51.6	4.9/4.8	20.2/20.2	348
2-fluorobenzylamino	54.4/54.1	4.8/4.8	18.7/18.4	376
3-fluorobenzylamino	54.4/53.9	4.8/4.7	18.7/18.2	376
4-fluorobenzylamino	54.4/54.3	4.8/4.8	18.7/18.3	376

2-chlorobenzylamino	52.1/52.0	4.6/4.7	17.9/17.5	392
3-chlorobenzylamino	52.1/51.9	4.6/4.6	17.9/17.3	392
4-chlorobenzylamino	52.1/51.8	4.6/4.5	17.9/17.1	392
2-bromobenzylamino	46.8/46.3	4.2/4.1	16.1/15.5	437
3-bromobenzylamino	46.8/47.8	4.2/4.5	16.1/15.6	437
4-bromobenzylamino	46.8/46.9	4.2/4.3	16.1/15.4	437
3-iodobenzylamino	42.3/42.4	3.8/3.9	14.5/14.6	484
2-methoxybenzylamino	55.8/55.9	5.5/5.3	18.1/17.9	388
3-methoxybenzylamino	55.8/55.5	5.5/5.7	18.1/18.0	388
4-methoxybenzylamino	55.8/55.6	5.5/5.5	18.1/18.1	388
2-hydroxybenzylamino	54.7/54.6	5.1/5.0	18.8/18.8	374
3-hydroxybenzylamino	54.7/54.5	5.1/5.1	18.8/18.5	374
4-hydroxybenzylamino	54.7/54.6	5.1/4.9	18.8/18.6	374
2,4-dichlorobenzylamino	47.9/47.8	4.0/4.1	16.4/16.5	427
3,4-dichlorobenzylamino	47.9/47.9	4.0/4.2	16.4/16.5	427
2,3-dihydroxybenzylamino	52.4/52.5	4.9/4.8	18.0/18.1	390
3,5-dihydroxybenzylamino	52.4/52.6	4.9/4.9	18.0/18.3	390
2-hydroxy-3-methoxybenzylamino	53.6/53.4	5.2/5.1	17.4/17.5	404
3-hydroxy-4-methoxybenzylamino	53.6/53.5	5.2/5.0	17.4/17.6	404
2,3-dimethoxybenzylamino	54.7/54.8	5.6/5.7	16.8/16.7	418
2,4-dimethoxybenzylamino	54.7/54.6	5.6/5.5	16.8/16.6	418
3,4-dimethoxybenzylamino	54.7/54.8	5.6/5.6	16.8/16.5	418
3,5-dimethoxybenzylamino	54.7/54.6	5.6/5.7	16.8/16.9	418

EXAMPLE 8: The synthesis of 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine in bench scale

- 5 *Feedstock:* 9- β -D-Arabinofuranosyl-hypoxanthine (1072 g, 4 mol), (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 2124 g (4.8 mol), dimethylformamide (DMF, 20 L, N,N-Diisopropyl-N-ethylamine (DIPEA, 1045 mL (6 mol), 3-methoxybenzylamine (658 g, 4.8 mol), demi water 40 l, 2-propanol 30 L.

10 *Procedure:*

Dimethylformamide (20 l) was placed into a glass duplicated reactor A1 equipped with thermometer (PT100) and reflux condenser. Reactor was filled in with inert atmosphere (nitrogen). Stirring with hopper opening was switched on. 9- β -D-arabinofuranosyl hypoxanthine and BOP (2124 g) were poured to the reactor using the respirator. As soon as

the solid is dissolved, DIPEA (1045 mL) and 3-methoxybenzylamine (658 g) were added. The reactor stayed under continuous mild nitrogen flow. Reaction mixture was heated (using duplication) to 50 °C, and was stirred for 20 hrs. Reaction course control: after 12 hrs of reaction, sample for TLC: 1 ml aliquot was diluted by 4 ml of methanol and the solution was applied next to the other starting compounds and standard product on TLC plate. TLC plate was evolved in the following mobile phase: chloroform:methanol:ammonium water solution; 4:1:0.05). If the reaction was still not finished, the mixture was further stirred at 50 °C, but next portion of BOP could be also added (200 g). If the reaction was finished (> 90 %), reaction mixture was cooled (via duplication) to the temperature of 20-25 °C and after that was reaction mixture drained into the transport vessel. Reactor was subsequently splashed with a small amount of methanol (3 x 1 L), and methanolic portions were mixed with reaction mixture). Reaction mixture was evaporated on rotary evaporator - a vacuum was secured by water ring vacuum pump - parameters such as pressure and temperature were established according to technology instructions. Distillation residue was (hot) drained into transport vessel. Evaporator was splashed with hot methanol - and this portion was evaporated using vacuum evaporator separately from the main portion. Reactor A1 was filled with demi water (40 L), stirring and cooling in duplication was switched on. Reactor was cooled to 10 °C and distillation residue was slowly added. Transport vessel was splashed with methanol (3 x 250 mL) and methanolic solution was also poured into the reactor. The reactor content was stirred for three hours at 10 - 15 °C. Emerging precipitate was filtered off on great Buchner funnel and washed first with cold water (+5 °C) then only by water (4 x 1 L). Crude product was dried in a convection oven at 80 °C. *Yield:* 1200 - 1250 g.

Crystallization of 6-(3-methoxybenzylamino)-9-β-D-arabinofuranosylpurine

Crude product: 1000 g, 2-propanol: 18 l, active carbon CXV 50 g

Procedure: 2-propanol (15 l) was poured into A1 reactor and stirring was switched on. Crude 6-(3-methoxybenzylamino)-9-β-D-arabinofuranosylpurine (1000 g) was added. The content of reactor was heated via duplication to 80 °C - the solid of crude product should be dissolved. If the product was not dissolved, it is necessary to continue stirring at 80 °C, or add next portion of 2-propanol. As soon as was all solid dissolved, active carbon was added and stirring is continued at 80 °C for 15 minutes. After that, the solution was

filtrated off using preheated Büchner channel (preheated in convection oven, 110 °C). Glass reactor was rinsed by 2-propanol (2 x 1 L) and filtration cake was washed with this portion of 2-propanol Büchner channel. Filtrate and flushing were merged together and placed into transport vessel for crystallization. Product crystallized at the temperature of +5
5 - +10 °C for 12 hrs. After the solid appeared, the product was filtrated off, rinsed with cold (+5 °C) 2-propanol (3 x 500 mL) and dried in convection oven at 70 °C to constant weight. *Yield*: 750 – 800 g, HPLC purity: > 98 %.

EXAMPLE 9: Synthesis of 6-(3-methoxybenzylamino)-9-β-D-2'-deoxyribofuranosylpurine

2'-deoxyinosine (252 mg) and BOP (531 mg) were dissolved in dry DMF (5 ml) and stirred at laboratory temperature under argon atmosphere. After five minutes, DIPEA (261 μl) and 3-methoxybenzylamine (167 μl) were added. Reaction mixture was stirred at laboratory temperature for 16 hrs. Reaction process was controlled via TLC (mobile phase:
15 chloroform-methanol-25% aqueous ammonia, 4 : 1 : 0.05). As soon as the conversion was not complete, next portion BOP (354 mg; 0.8 mmol) was added and reaction mixture was heated to 60 °C and stirred for 6 hrs. As soon as there were not detected a spot of starting 2'-deoxyinosine, reaction mixture was evaporated using vacuum evaporator (maximal temperature 55 °C). A residue (cca 1.5 g) was chromatographically purified using silica
20 gel (150 g); mobile phase: 0-20 % methanol in dichlormethane. *Yield*: 270 mg (79 %), *HPLC-MS purity*: 98+%, [M+H⁺] 372, mp 165-170 °C, C/H/N: 58,2/58,1; 5,7/5,7; 18,9/18,8; ¹H(DMSO-*d*₆, 300 MHz) δ ppm: 2.25-2.37 (m, 1H), 2.45-2.64 (m, 1H), 3.50-3.68 (m, 2H), 3.70 (s, 3H), 3.85-3.90 (m, 1H), 4.33-4.45(m, 1H), 4.67 (bs, 2H), 4.85 (t, 1H), 5.10 (d, *J* = 4.0 Hz), 6.30 (t, *J* = 6.9 Hz), 6.77 (d, *J* = 7.1 Hz), 6.89 (s, 1H), 6.91 (s,
25 1H), 7.20 (t, *J* = 7.6 Hz), 8.19 (s, 1H), 8.21 (s, 1H), 8.34 (bs, 1H).

EXAMPLE 10: Synthesis of 6-(2-hydroxybenzylamino)-9-β-D-2'-deoxyribofuranosylpurine

2'-deoxyinosine (252 mg) and BOP (664 mg) were dissolved in dry DMF (8 ml) and stirred at laboratory temperature under argon atmosphere. After five minutes, DIPEA (348 μl) and 2-hydroxybenzylamine (131 μl) were added. Reaction mixture was stirred at 50 °C for 20

hrs. Reaction process was controlled via TLC (mobile phase: chloroform-methanol-25% aqueous ammonia, 4 : 1 : 0.05). As soon as the conversion was not complete, next portion BOP (354 mg; 0.8 mmol) was added and reaction mixture was heated to 60 °C and stirred for 10 hrs. As soon as there were not detected a spot of starting 2'-deoxyinosine, reaction mixture was evaporated using vacuum evaporator (maximal temperature 55 °C). A residue (cca 1.5 g) was chromatographically purified using silica gel (150 g); mobile phase: 0-20 % methanol in dichlormethane. *Yield*: 250 mg (70 %), *HPLC-MS purity*: 98+%, $[M+H^+]$ 358, mp 172-175 °C, C/H/N: 57,1/57,2; 5,3/5,4; 19,6/19,2; $^1H(DMSO-d_6, 300\text{ MHz})$ δ ppm: 3.66 (s, 2H), 3.78 (s, 1H), 4.15 (s, 2H), 4.63 (bs 2H), 5.12 (s, 1H), 5.55 (s, 1H), 5.64 (s, 1H), 6.28 (s, 1H), 6.58 (d, $J = 7.5\text{ Hz}$), 6.73 (s, 1H), 6.76 (s, 1H), 7.07 (t, $J = 7.5\text{ Hz}$), 8.19 (s, 1H), 8.21 (s, 1H), 9.27 (bs, 1H).

EXAMPLE 11: Synthesis of 6-(2-hydroxy-3-methoxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine

2'-deoxyinosine (252 mg) and BOP (664 mg) were dissolved in dry DMF (10 ml) and stirred at 50 °C. After five minutes, DIPEA (348 μ l) and 2-hydroxy-3-methoxybenzylamine (165 μ l) were added. Reaction mixture was stirred at laboratory temperature for at least 20 hrs. Reaction process was controlled via TLC (mobile phase: chloroform-methanol-25% aqueous ammonia, 4 : 1 : 0.05). As soon as the conversion was not complete, next portion BOP (354 mg; 0.8 mmol) was added and reaction mixture was heated to 70 °C and stirred for 6 hrs. As soon as there were not detected a spot of starting 2'-deoxyinosine, reaction mixture was evaporated using vacuum evaporator (maximal temperature 55 °C). A residue (cca 1.5 g) was chromatographically purified using silicagel (150 g); mobile phase: 0-20 % methanol in dichlormethane. *Yield*: 270 mg (79 %), *HPLC-MS purity*: 98+%, mp 174-178 °C, $[M+H^+]$ 388, C/H/N: 55,8/55,3; 5,5/5,6; 18,1/18,2; $^1H(DMSO-d_6, 300\text{ MHz})$ δ ppm: 2.25-2.37 (m, 1H), 2.45-2.64 (m, 1H), 3.50-3.68 (m, 2H), 3.77 (s, 3H), 3.85-3.90 (m, 1H), 4.33-4.45(m, 1H), 4.67 (bs, 2H), 4.85 (t, 1H), 5.10 (d, $J = 4.0\text{ Hz}$), 5.39 (d, $J = 6.0\text{ Hz}$), 6.30 (t, $J = 6.9\text{ Hz}$), 6.77 (d, $J = 7.1\text{ Hz}$), 6.89 (s, 1H), 7.20 (t, $J = 7.6\text{ Hz}$), 8.19 (s, 1H), 8.21 (s, 1H), 8.34 (bs, 1H).

EXAMPLE 12: Synthesis of 6-(furfurylamino)-9- β -D-2'-deoxyribofuranosylpurine

2'-deoxyinosine (252 mg) and BOP (670 mg) were dissolved in dry DMF (10 ml) and stirred at laboratory temperature under argon atmosphere. After five minutes, DIPEA (350 μ l) and furfurylamine (150 μ l) were added. Reaction mixture was stirred at 60 °C for at least 10 hrs. Reaction process was controlled via TLC (mobile phase: chloroform-methanol-25% aqueous ammonia, 4 : 1 : 0.05). As soon as the conversion was not complete, next portion BOP (354 mg; 0.8 mmol) was added and reaction mixture was heated to 70 °C and stirred for 6 hrs. As soon as there were not detected a spot of starting 2'-deoxyinosine, reaction mixture was evaporated using vacuum evaporator (maximal temperature 55 °C). A residue (cca 1.5 g) was chromatographically purified using silica gel (150 g); mobile phase: 0-20 % methanol in dichlormethane. *Yield*: 300 mg (82 %), *HPLC-MS purity*: 98+%, $[M+H]^+$ 332, C/H/N: 54,4/54,3; 5,2/5,2; 19,3/19,5¹H(DMSO-*d*₆, 300 MHz) δ ppm: 3.61-3.72 (m, 2H), 3.78 (d, *J* = 3.9 Hz), 4.14 (s, 2H), 4.69 (bs, 2H), 5.11 (t, *J* = 5.4 Hz), 5.54 (d, *J* = 3.9 Hz), 5.62 (d, *J* = 4.8 Hz), 6.22 (d, *J* = 2.7 Hz), 6.27 (d, *J* = 4.2 Hz), 6.36 (t, *J* = 3.0 Hz), 7.54 (s, 1H), 8.21 (s, 3H).

Table 2: 6-substituted-9- β -D-2'-deoxyribofuranosylpurines prepared according to examples 9-12

Substituent in position 6 (-NH-Ar)	Elemental analysis calculated/found			ES-MS [$M+H^+$]
	%C	%H	%N	
4-methylfurfurylamino	55.6/55.5	5.5/5.6	18.5/18.4	346
5-methylfurfurylamino	55.6/55.4	5.5/5.6	18.5/18.3	346
4-hydroxyfurfurylamino	51.9/51.8	4.9/5.0	20.2/20.1	348
5-hydroxyfurfurylamino	51.9/52.0	4.9/4.8	20.2/20.2	348
3-chlorobenzylamino	54.3/54.2	4.8/4.8	18.6/18.6	376
4-chlorobenzylamino	54.3/54.3	4.8/4.9	18.6/18.5	376
2-bromobenzylamino	48.6/48.7	4.3/4.4	16.7/16.7	421
3-bromobenzylamino	48.6/48.6	4.3/4.5	16.7/16.8	421
4-bromobenzylamino	48.6/48.3	4.3/4.3	16.7/16.9	421
2-methoxybenzylamino	58.2/58.3	5.7/5.5	18.9/18.6	372
3-methoxybenzylamino	58.2/58.1	5.7/5.9	18.9/18.7	372
2-hydroxybenzylamino	57.1/57.2	5.4/5.3	19.6/19.8	358
3-hydroxybenzylamino	57.1/57.3	5.4/5.3	19.6/19.5	358
4-hydroxybenzylamino	57.1/57.1	5.4/5.2	19.6/19.5	358
2,3-dihydroxybenzylamino	54.7/54.5	5.1/5.2	18.8/18.7	374

3,5-dihydroxybenzylamino	54.7/54.8	5.1/5.3	18.8/18.6	374
2-hydroxy-3-methoxybenzylamino	55.8/55.7	5.5/5.6	18.1/18.2	388
3-hydroxy-4-methoxybenzylamino	55.8/55.6	5.5/5.7	18.1/18.3	388
2,3-dimethoxybenzylamino	56.9/56.8	5.8/5.7	17.5/17.4	402
2,4-dimethoxybenzylamino	56.9/56.9	5.8/5.6	17.5/17.5	402
3,4-dimethoxybenzylamino	56.9/56.8	5.8/5.9	17.5/17.7	402
3,5-dimethoxybenzylamino	56.9/56.9	5.8/5.9	17.5/17.8	402

EXAMPLE 13: Evaluation of cytotoxicity of novel derivatives for skin cell by MTT in vitro test

MTT assay is a standard test of toxicity based on photometric measurement of the ability of metabolically active cells to reduce MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). Using the assay, the effects of 72 hour treatments with several concentrations of the compounds (sixfold dilution, maximal concentration = 50 microM) on viability of skin fibroblasts BJ and keratinocytes HaCaT were evaluated. About 5,000 cells were seeded per well of a 96-well plate 24 hours before the treatment. DMSO vehiculum was used as a negative control. After 72 hour treatment, new medium with MTT (Sigma, M2128) was added to a final concentration of 0.5 mg/ml. After 3 hours, medium was removed and resulting formazan in the cells was dissolved in DMSO. The absorbance was measured at 570 nm (640 nm reference wavelength). The IC₅₀ values were calculated from the dose-response curves. 6-Benzylaminopurine riboside and 6-furfurylaminopurine riboside were used as positive controls – they were toxic in the MTT test. The following results were obtained.

	IC ₅₀ (μM)
dimethylsulfoxide	>50
6-benzylamino-9-β-D-arabinofuranosylpurine	>50
6-furfurylamino-9-β-D-arabinofuranosylpurine	>50
6-(3-methoxybenzylamino)-9-β-D-arabinofuranosylpurine	>50
6-(2-chlorobenzylamino)-9-β-D-arabinofuranosylpurine	>50
6-(3-hydroxybenzylamino)-9-β-D-arabinofuranosylpurine	>50
6-(3-chlorobenzylamino)-9-β-D-arabinofuranosylpurine	>50

6-(2,3-dimethoxybenzylamino)-9- β -D-arabinofuranosylpurine	49
6-(2,3,4-trimethoxybenzylamino)-9- β -D-arabinofuranosylpurine	48
6-(3-iodobenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(3-aminobenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(furfurylamino)-9- β -D-2'-deoxyribofuranosylpurine	>50
6-(2-hydroxybenzylamino)-9- β -D-2'-deoxyribofuranosylpurine	>50
6-benzylaminopurin9-ribosylpurine (comparative example)	≤ 3
6-furfurylamino-9-ribosylpurine (comparative example)	≤ 3

EXAMPLE 14: SRB in vitro toxicity test

SRB (sulforhodamine B) assay is a standard toxicity test based on a photometric measurement of the cellular protein content after the staining with sulphorhodamine B.

- 5 Using the assay, the effects of 72 hour treatments with several concentrations of the compounds (sixfold dilution, maximal concentration = 50 microM) on viability of skin fibroblasts BJ and keratinocytes HaCaT were evaluated. About 5,000 cells were seeded per well of a 96-well plate 24 hours before the treatment. DMSO vehiculum was used as a negative non-toxic control. 6-benzylaminopurine riboside a 6-furfurylamino purin riboside
- 10 were used as positive toxic controls. After three days the medium was removed and the cells fixed with 10% (wt/vol) trichloroacetic acid. After the extensive washing in distilled water, 0.4% (wt/vol) solution of SRB in acetic acid was added and the fixed cells were stained for 30 minutes. The unbound stain was washed away by distilled water and the bound SRB was solubilized in unbuffered 10 mM Tris base. Absorbance was measured at
- 15 564 nm. IC50 values were calculated from dose-response curves.

The following results were obtained:

	IC 50 (μ M)
dimethylsulfoxide	>50
6-benzylaminopurine-9- β -D-arabinofuranosylpurine	>50
6-furfurylamino-9- β -D-arabinofuranosylpurine	>50
6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(2-chlorobenzylamino)-9- β -D-arabinofuranosylpurine	>50

6-(3-hydroxybenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(3-chlorobenzylamino)-9- β -D-arabinofuranosylpurine	48
6-(3-iodobenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(3-aminobenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(furfurylamino)-9- β -D-2'-deoxyriboside	>50
6-(2-hydroxybenzylamino)-9- β -D-2'-deoxyriboside	>50
6-(2,3-dimethoxybenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-(2,3,4-trimethoxybenzylamino)-9- β -D-arabinofuranosylpurine	>50
6-furfurylamino-9-ribosylpurine (comparative example)	≤ 3

EXAMPLE 15: One-step growth curve for the compound 6-(benzylamino)purine-9- β -D-arabinofuranosylpurine

The experiments were performed with BJ skin fibroblasts in 24-well tissue culture plates.

- 5 About 10,000 cells in culture medium comprising DMEM with 10 % FBS were seeded into the individual wells. The cells were allowed to attach for 24 hours. The test compound was added to final concentrations in a range from 12.5 to 100 μ M. DMSO vehiculum was also tested. In order to control for variability, two plate columns (A,D) were treated with DMSO vehiculum. The culture medium with the test chemicals or DMSO
- 10 vehiculum was changed twice a week. Following trypsinization, the numbers of cells in 4 wells for each concentration were counted using Coulter counter on 7th and 14th day. The obtained results are showed in Fig. 1. The tested compound did not have a negative influence on cell viability.

- 15 EXAMPLE 16: In vitro test of skin irritation in EpiDERMTM

EpiDERMTM is a 3D model of epidermis manufactured by Mattek company. The effects of tested substances are evaluated by MTT. 2 solutions (2 application forms) of the compounds 6-furfurylamino-9- β -D-arabinofuranosylpurine and 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine in concentrations 1 mM and 200

20 microM in 0,5% DMSO/99,5% PBS were evaluated according to a standard protocol "INVITRO EpiDermTM SKIN IRRITATION TEST". After a preincubation of the tissues,

30 microliters of the application form – solution were applied on the individual tissues. The exposition time was 60 minutes. Three tissues were used for each tested concentration as well as for controls. Following washing out of the applied solution, the tissues were incubated for 42 hour in order to allow a reparation of possible damage. In the next step, the tissue was incubated with MTT for 3 hours. The resulting formazan was extracted to isopropanol. Relative viability of the individual tissues was calculated as a percentage of viability of the average of the negative controls. Average viability of the tissues treated with 1 mM solution of the test substance was 99.3 % for the compound 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine and 98.0 % for the compound 6-(furfurylamino)-9- β -D-arabinofuranosylpurine where 100 % is an average viability of the tissues treated with the solvent only. None of the tested compounds in any of the concentrations caused any tissue damage or irritation.. The compounds were evaluated as non-irritant in the tested concentrations. This result is favorable for the intended use of the compounds in cosmetics.

EXAMPLE 17: Evaluation of eye irritation in EpiOcular™

EpiOcular is a model of corneal epithelium manufactured by Mattek company. The effect of the tested substances is evaluated by MTT. A substance is considered irritant/corrosive if the absorbance of the formazane created by reduction of MTT is lower than 60 percent of value for negative control. Solutions (250 a 500 microM) of compounds 6-benzylamino-9- β -D-arabinofuranosylpurine, 6-furfurylamino-9- β -D-arabinofuranosylpurine and 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurin in the medium from the EpiOcular kit were tested in duplicates. The medium served as a negative control. The test was carried out according the manufacturer`s manual – the protocol for testing of liquid application forms. Only incubation time was increased from 30 min to 18 hours. The procedure is summarized below. After the delivery, the tissues were left in laboratory temperature for 15 min. After the integrity control and removal of agarose, the tissues were transferred into the wells of the 6-well plates containing 1 ml of cultivation medium. After 1 hour, the medium was exchanged for fresh one and the tissues were cultivated for 18 hours. Subsequently 20 microliters of DPBS without Ca²⁺ and Mg²⁺ (a component of the kit) was applied on the tissues, followed by 50 microliters of test solutions. After 18 hour incubation time, the

tissues were removed from cultivation plate and washed out repeatedly in an excess of DPBS without $\text{Ca}^{2+}/\text{Mg}^{2+}$ (3 beakers with 100 ml). Subsequently the tissues were transferred to the wells of 12-well plates with 5 ml tempered medium and incubated for 12 minutes. After that, the tissues were transferred into the wells of 6-well plate with 1 ml of medium and incubated for 2 hours. Three hour incubation with MTT solution (1 mg/ml) was carried out in 24-well plates (0.3 ml of medium per well). After the incubation, the tissues were transferred to a new 24-well plate with 2 ml isopropanol per well. The plate was placed on a shaker and the resulting formazan was extracted for 3 hours. 200 microliters of the extracts were transferred to 96-well plate. Absorbance was measured at 570 nm and related to that of the negative control. All the tissue manipulation before the isopropanol extraction was carried out in sterile conditions. The cultivation was done in the standard cultivation conditions (CO_2 5,5 procent, 37°C), the cultivation medium and DPBS without Ca^{2+} and Mg^{2+} ions.

Conclusion: The relative viability of the tissues treated with the test compounds was 98-103 %. The compounds in the tested concentration range do not cause irritation and can be favorably used in cosmetics including preparations that could be applied on face and the area around eyes.

EXAMPLE 18: Anti-senescent activity of novel compounds tested in senescent bioassay on wheat leaf segments

Seeds of winter wheat, *Triticum aestivum* cv. Hereward, were washed under running water for 24 hours and then sown on vermiculite soaked with Knop's solution. They were placed in the growth chamber at 25°C with a 16/8 h light period at $50\ \mu\text{mol}\cdot\text{m}^{-2}\cdot\text{s}^{-1}$. After 7 days, the first leaf was fully developed and the second leaf had started to grow. A tip section of the first leaf, approximately 35 mm long, was removed from 5 seedlings and trimmed slightly to a combined weight of 100 mg. The basal ends of the five leaf tips were placed in the wells of a microtiter polystyrene plate containing 150 μL of the tested derivative solution each. The entire plate was inserted into a plastic box lined with paper tissues soaked in distilled water to prevent leaf sections from drying out. After 96 h incubation in the dark at 25°C , the leaves were removed and chlorophyll extracted by heating at 80°C for 10 min in 5 mL of 80% ethanol (v/v). The sample volume was then restored to 5 mL by the

addition of 80% ethanol (v/v). The absorbance of the extract was recorded at 665 nm. In addition, chlorophyll extracts from fresh leaves and leaf tips incubated in deionised water were measured. The results are means of five replicates and the entire test was repeated twice. In each experiment activities of the novel compounds were tested and compared with activity of BAP, which is known to be highly active cytokinin.

The compounds to be tested were dissolved in dimethylsulfoxide (DMSO) and the solution brought up to 10^{-3} M with distilled water. This stock solution was further diluted with the respective media used for the biotest to a concentration ranging from 10^{-8} M to 10^{-4} M. The final concentration of DMSO did not exceed 0.2 % and therefore did not affect the biological activity in the assay system used. The activity obtained for 10^{-4} M of BAP was postulated as 100 %.

Newly developed compounds possess very strong antisenescence properties. Some of them cause 200% increase of chlorophyll content in detached wheat leaves in comparison to BAP.

Tab. 3: The effect of novel compounds on delaying senescence in detached leaf segments of *Triticum aestivum* cv. Hereward. The results are expressed in % of initial content of chlorophyll in fresh leaves before incubation.

Compound	maximum effective concentration (mol.l ⁻¹)	activity (%) [10 ⁻⁴ mol.l ⁻¹ BAP = 100%]
6-furfurylamino-9-β-D-arabinofuranosylpurine	10 ⁻⁴	193±1
6-(3-methoxybenzylamino)-9-β-D-arabinofuranosylpurine	10 ⁻⁴	118±2
6-benzylaminopurine-9 β-D-deoxyribosylpurine	10 ⁻⁴	178±9
6-(3-chlorobenzylamino)-9-β-D-arabinofuranosylpurine	10 ⁻⁴	172±8
6-(3-fluorobenzylamino)-9-β-D-arabinofuranosylpurine	10 ⁻⁴	195±6
6-(2-bromobenzylamino)-9-β-D-arabinofuranosylpurine	10 ⁻⁵	186±19
6-(3-bromobenzylamino)-9-β-D-arabinofuranosylpurine	10 ⁻⁴	198±10
6-(4-bromobenzylamino)-9-β-D-arabinofuranosylpurine	10 ⁻⁴	176±11

6-(3-iodobenzylamino)-9-β-D-arabinofuranosylpurine	10^{-4}	198±4
6-(3,4-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine	10^{-4}	147±6
6-(3-chlorobenzylamino)-9-ribose (comparative example)	10^{-4}	72±8
6-(3-iodobenzylamino)-9-ribose (comparative example)	10^{-4}	58±19
6-(3-bromobenzylamino)-9-ribose (comparative example)	10^{-4}	89±10
6-(3,4-dimethoxybenzylamino)-9-ribose (comparative example)	10^{-4}	47±6
6-(2,4-dichlorobenzylamino)-9-ribose (comparative example)	10^{-4}	5±1

EXAMPLE 19: *In vitro* cytotoxic activity of new derivatives on cancer cell lines

One of the parameters used as the base for cytotoxic analysis is metabolic activity of viable cells, such as microtiter assay, which uses the Calcein AM, is now widely used to quantitate cell proliferation and cytotoxicity. The quantity of reduced Calcein AM corresponds to the number of viable cells in culture. The cell lines of breast cancer (MCF-7), mouse fibroblasts (NIH3T3), human erythroleukemia (K562) were used for routine screening of cytotoxicity of the compounds. The cells were maintained in Nunc/Corning 80 cm² plastic bottles and grown in media for cell culture (DMEM containing 5g/l of glucose, 2mM of glutamin, 100 U/ml of penicilin, 100 µg/ml of streptomycin, 10% of fetal bovine serum and sodium hydrogencarbonate). Cell suspensions were diluted according to cell types and according to expected final cell density (10^4 of cells per well according to characteristics of cell growth), pipetted 80 µl of cell suspension on 96-well microtiter plates.. Inoculates were stabilized by 24 hrs preincubation at 37°C in CO₂. Particular concentrations of tested compounds were added in time zero as 20 µl aliquotto wells of microtiter plates. Usually, the compounds were diluted into six concentrations in four-fold dilution series. In routine testing, the highest well concentration was 166.7 µM, of change dependent on the substance. All drug concentrations were examined in duplicates .The incubation of cells with tested derivatives lasted 72 hrs at 37°C, 100 % humidity and in the atmosphere of CO₂. At the end of the incubation period, the cells were tested and analysed according to the addition of Calcein AM (Molecular probes) solution and the incubation

lasted for next 1 hour. Fluorescence (FD) was measured using Labsystem FIA reader Fluorskan Ascent (Microsystems). The survival of tumor cells (The tumor cell survival-TCS) was counted according to equation: $GI_{50} = (FD_{\text{well with derivative}} / FD_{\text{control well}}) \times 100 \%$. The value of GI_{50} , that is equal to the concentration of compound at which 50 % of tumour cells are terminated. To evaluate the antitumor activity was tested toxicity of new derivatives on panel of cell lines of different histogenetic and species origin (Tab. 7 , GI_{50} concentration given in μM) . It turned out that new compounds showed to be non toxic for neither of all tested tumor lines nor for nonmalignant cell line NIH3T3. Effective derivatives killed tumor cells in concentrations close to 0.1 to 50. None of the newly prepared compounds only reached the value.

Tab. 4. Cytotoxicity of newly prepared compounds for various tumour cell lines and NIH3T3

Compound	MCF-7	K562	NIH3T3
6-benzylamino-9-ribosylpurine (comparative example)	5.4	5.5	39
6-benzyl-9- β -D-arabinofuranosylpurine	>100	>100	>100
6-furfuryl-9- β -D-arabinofuranosylpurine	>100	>100	>100
6(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine	>100	>100	>100
6-benzylamino-9- β -D-deoxyribosylpurine	>100	>100	>100
3-methylbenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100
4-methylbenzylamino-9- β -D-arabinofuranosylpurine	95	>100	>100
2-methylbenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100
3-fluorobenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100
4-chlorobenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100
2-fluorobenzylamino-9- β -D-arabinofuranosylpurine	87	>100	>100
3-chlorobenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100
4-hydroxybenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	87
3-fluorobenzylamino-9- β -D-2'-	>100	>100	>100

deoxyribosylpurine			
3-chlorobenzylamino-9- β -D-2'-deoxyribosylpurine	>100	>100	>100
3-hydroxybenzylamino-9- β -D-2'-deoxyribosylpurine	>100	>100	>100
2,4-dimethoxybenzylamino-9- β -D-arabinofuranosylpurine	98	>100	>100
2-chloro-4-fluorobenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100
3-chloro-4-fluorobenzylamino-9- β -D-arabinofuranosylpurine	>100	>100	>100

EXAMPLE 20. *In vitro* test of phototoxic effects of 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine on normal human dermal fibroblasts

5

Phototoxic potential of test compound was determined by modified *in vitro* test validated phototoxicity evaluation (Spielmann H, Balls M, Dupuis J, Pape WJ, Pechovitch G, de Silva O, Holzhütter HG, Clothier R, Desolle P, Gerberick F, Liebsch M, Lovell WW, Maurer T, Pfannenbecker U, Potthast JM, Csato M, Sladowski D, Steiling W, Brantom P.,
 10 Toxicol In Vitro. **1998** Jun 1;12(3):305-27). Normal human dermal fibroblasts (NHDF) were used as an *in vitro* model. Cells were isolated from tissue specimens obtained from healthy patients undergoing plastic surgery at the Department of Plastic and Aesthetic Surgery (University Hospital Olomouc). The use of skin tissue was in accordance with the Ethics Committee of the University Hospital and Faculty of Medicine and Dentistry,
 15 Palacký University, Olomouc and all patients signed written informed consent. Fibroblasts were used between the 2nd and 4th passage. For all experiments the fibroblasts were seeded onto 96-well plates at a density of 0.8×10^5 cells/ml (0.2 ml per well) of cultivation medium (DMEM supplemented with foetal calf serum (10%, v/v), penicillin (100 mg/ml) and streptomycin (100 U/ml)).

20 Test compound was 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine. Compound was dissolved in DMSO and then diluted in serum free medium (DMEM supplemented with penicillin (100 mg/ml) and streptomycin (100 U/ml)). The final applied concentrations of the compound 0.39-125 μ mol/l. As a control, serum free medium supplemented with appropriate concentration of DMSO (0.5 %, v/v) was used. In parallel
 25 with test compounds, chlorpromazine (CPZ; 0.39-100 μ mol/l) was used as a known

phototoxic compound. The test compound was in parallel applied on two 96-well plates with NHDF. After 60 minutes incubation with test compound medium was discarded, cells were washed two-times with PBS and PBS supplemented with glucose (1 mg/ml) was applied. A plate was then exposed to a non-cytotoxic dose of UVA radiation (5.0 J/cm²) using a solar simulator SOL 500 (Dr. Hoenle Technology, Germany) equipped with a H1 filter transmitting wavelengths of 320-400 nm. Intensity of UVA radiation was evaluated before each irradiation by UVA-meter. A control (non-irradiated) plate was for the period of irradiation incubated in dark. After UVA exposure PBS with glucose was discarded and serum free medium was applied. After 24 hours (37 °C, 5 % CO₂) cell damage was evaluated by neutral red (NR) incorporation into viable cells. Medium was discarded and NR solution (0.03% w/v, PBS) was applied. After 60 minutes NR solution was discarded, cells were fixed with a mixture of formaldehyde (0.5%, v/v) and CaCl₂ (1 %, m/v) in ratio 1:1 and then NR was dissolved in methanol (50%, v/v) with acetic acid (1%, v/v). After 5 minutes of intensive shaking absorbance was measured at 540 nm. Experiments were performed in four independent repetition with use of cells from four donors to minimize individual sensitivity of donor cells. Phototoxic effect was evaluated as % of viability of control cells that was calculated from experimental data (absorbance) according to the following equation:

$$\text{Viability (\% of control)} = \left(\frac{(A_S - A_B)}{(A_C - A_B)} \right) \cdot 100$$

A_S ... absorbance of sample (cells pre-incubated with test compound in serum free medium and irradiated)

A_C ... absorbance of control (cells pre-incubated with DMSO in serum free medium and irradiated)

A_B ... absorbance of background (extraction solution)

Result: Treatment with test compounds and following exposure to non-toxic UVA dose did not cause decrease in cell viability ~ incorporation of NR and thus test compound can be considered as non-phototoxic in the used concentration range (0.9-125 µmol/l or 3.9-500 µmol/l). Results are given in Fig. 3. Effect of a well-known phototoxic compound chlorpromazine (Spielmann H, Balls M, Dupuis J, Pape WJ, Pechovitch G, de Silva O, Holzhütter HG, Clothier R, Desolle P, Gerberick F, Liebsch M, Lovell WW, Maurer T,

Pfannenbecker U, Potthast JM, Csato M, Sladowski D, Steiling W, Brantom P., Toxicol In Vitro. **1998** Jun 1;12(3):305-27), used as positive control is demonstrated in Fig. 4. Above data indicate that test compounds are safe for cosmetic and dermatological application including use with following exposure of treated skin with solar radiation.

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EXAMPLE 21: *In vitro* test of photoprotective effects of 6(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine on dermal fibroblasts

Normal human dermal fibroblasts (NHDF) were used as an *in vitro* model. Cells were
10 isolated from tissue specimens obtained from healthy patients undergoing plastic surgery at the Department of Plastic and Aesthetic Surgery (University Hospital Olomouc). The use of skin tissue was in accordance with the Ethics Committee of the University Hospital and Faculty of Medicine and Dentistry, Palacký University, Olomouc and all patients signed written informed consent. Fibroblasts were used between the 2nd and 4th passage. For all
15 experiments the fibroblasts were seeded onto 96-well plates at a density of 0.8×10^5 cells/ml (0.2 ml per well) of cultivation medium (DMEM supplemented with foetal calf serum (10%, v/v), penicillin (100 mg/ml) and streptomycin (100 U/ml)).

Test compounds included 6-(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine. Compounds were dissolved in DMSO and then diluted in serum free medium (DMEM
20 supplemented with penicillin (100 mg/ml) and streptomycin (100 U/ml)). The final applied concentrations of 6(3-methoxybenzylamino)-9- β -D-arabinofuranosylpurine were 0,9; 1,8; 3,9 a 7,8 $\mu\text{mol/l}$. As a control serum free medium supplemented with appropriate concentration of DMSO (0.5 %, v/v) was used. Each test compound was in parallel applied on two 96-well plates with NHDF. After 60 minutes incubation medium with test
25 compound was discarded, cells were washed two-times with PBS and PBS supplemented with glucose (1 mg/ml) was applied. To study UVA photoprotection, a plate was exposed to a cytotoxic dose of UVA radiation (7.5 J/cm^2) using a solar simulator SOL 500 (Dr. Hoenle Technology, Germany) equipped with a H1 filter transmitting wavelengths of 320-400 nm. To study UVB photoprotection, a plate was exposed to a cytotoxic dose of UVB
30 radiation (400 mJ/cm^2) using the solar simulator equipped with a H2 filter transmitting wavelengths of 295-320 nm. Intensity of UVA or UVB radiation was evaluated before each irradiation by UVA- or UVB-meter. Control (non-irradiated) plates were for the period of

irradiation incubated in dark. After UVA or UVB exposure PBS with glucose was discarded and serum free medium was applied. After 24 hours (37 °C, 5 % CO₂) cell damage was evaluated by neutral red (NR) incorporation into viable cells. Medium was discarded and NR solution (0.03% w/v, PBS) was applied. After 60 minutes NR solution was discarded, cells were fixed with a mixture of formaldehyde (0.5%, v/v) and CaCl₂ (1 %, m/v) in ratio 1:1 and then NR was dissolved in methanol (50%, v/v) with acetic acid (1%, v/v). After 5 minutes of intensive shaking absorbance was measured at 540 nm. Experiments were performed in four independent repetition with use of cells from four donors to minimize individual sensitivity of donor cells. Photoprotective effect was evaluated by comparison of experimental data (absorbance) of test compounds with a positive control and a negative control (according to the following equation:

$$\text{Protection (\%)} = 100 - \left| \frac{As - Anc}{Apc - Anc} \right| \cdot 100$$

As ... absorbance of sample (cells pre-incubated with test compounds in serum free medium and irradiated)

Anc ... absorbance of negative control (cells pre-incubated with s DMSO in serum free medium and non-irradiated = incubated in dark)

Apc ... absorbance of positive control (cells pre-incubated with s DMSO in serum free medium and irradiated)

Results: Cells pre-incubated with test compounds and exposed to UVA or UVB radiation showed higher viability (ability to incorporate NR) compared to those pre-incubated with DMSO (control) and UVA or UVB irradiated (Fig. 5 and 6). Therefore test compound has high photoprotective potential.

EXAMPLE 19: Differential gene expression study

Comparative gene expression analysis in Arabidopsis model was performed to gain information about the reprogramming of gene transcription when senescent leaves were treated with 6-(3-methoxybenzylamino)-9-β-D-arabinofuranosylpurine (3MeOBAPA).

For isolation of total RNA, Arabidopsis wild-type plants (Col-0) were used, which were either treated with 3MeOBAPA or left untreated. Wild-type plants were grown in soil for 30 days, and then leaves of similar size and chlorophyll content were cut and immediately used for the treatment. At least 20 detached leaves were submerged in 1 x MS medium

supplemented with 10 μ M 3MeOBAPA. Control samples were mock treated with DMSO only. After incubation for 6 h or 48 h in the dark, detached leaves were frozen in liquid nitrogen and used for RNA isolation; 150 mg of liquid nitrogen-ground material was used per isolation. cDNA sequencing libraries were prepared with the Illumina TruSeq Stranded mRNA LT Sample Prep Kit (Illumina, San Diego, CA) according to standard Illumina's protocols and sequenced on HiSeq 2500 apparatus (50 bp single-end reads).

Data were subjected to differential transcriptomic analysis with the aim to reveal significantly regulated genes and their expression levels. To gain insight into the molecular mechanism of 3MeOBAPA action in Arabidopsis we decided to analyze the gene expression patterns *via* comparison of mock (DMSO)-treated plants with those obtained after i) short time treatment with 3MeOBAPA (6 h) and ii) long time treatment (48 h). This comparison leads to identification of group of genes with similar kinetic of expression and helps to understand possible mechanism of regulation. For data analysis, we performed *ab initio* method where sequencing reads were mapped to the reference genome. The short time treatment resulted in reprogramming of the gene transcription compared to the mock-treated control with 1119 downregulated and 1102 upregulated genes ($P \leq 0.05$). Further treatment with 3MeOBAPA (i.e. 48 h) led to alterations in the expression profiles and, thus, we could observe more profound changes in the numbers of affected genes: 7 095 genes were downregulated and 7509 genes were upregulated ($P \leq 0.05$). Analysis of regulated genes in both groups (short time treatment vs. long time treatment) showed a substantial overlap in the two categories. Indeed, we could detect 1102 genes that were upregulated in response to 3MeOBAPA treatment and 724 genes that were downregulated in both groups (Fig. 7). The overlap is particularly visible in the group of upregulated genes suggesting a rapid response to the elicitation after 6 h treatment that reaches maximal values after 48 h incubation with 3MeOBAPA. This trend is well documented in the list of top 50 genes upregulated in response to 3MeOBAP treatment (Tab. 1). As evident, all genes that were upregulated after 6h of the treatment probably remain activated over a period of 48 h and their expression levels in the latter time point are one or two orders of magnitude higher than those recorded in 6h.

A closer inspection of the top 50 3MeOBAPA upregulated genes reveals that several most abundant gene transcripts present in both groups are related directly to plant defense mechanisms (Tab. 5). This was the case of plant defensins family proteins including

At5g44430 coding for defensin-like protein 1.2C, At5g44420 coding for defensin-like protein 1.2A, At2g26020 coding for defensin-like protein 1.2B or At2g26010 coding for defensin-like protein 1.3 which are important anti-stress factors upregulated in response to pathogen or stress elicitation and, importantly, also during plant senescence. Moreover, we also detected high expression levels of several enzymes involved in modifications and in remodeling of cell wall that are also important for pollen tube growth. These enzymes belong either to pectin methylesterase or pectin lyase families, such as At2g47040 coding for pectin methylesterase Vanguard1 and At3g07820 coding for pectin lyase-like superfamily protein, or, interestingly, there were also genes coding for enzymes with combined pectin methylesterase/pectin methylesterase inhibitor activity such as At2g47050 or At3g05610. Other enzymes of cell wall synthesis were also detected such as products of gene At4g35010 coding for β -galactosidase 11 (BGAL11), At1g02790 coding for polygalacturonase 4 (PGA4) or At3g62710 coding for glycosyl hydrolase family protein. This strongly suggests that in plants 3MeOBAP specifically regulates processes that are necessary for cell wall remodeling and consequent enhanced resistance to stresses and fungal pathogens.

Table 5.

Top 50 genes upregulated in response to 3MeOBAPA treatment in two selected time points. Genes with $P \leq 0.05$ that are changed both after 6h and after 48h of treatment with 10 μ M 3MeOBAP are shown.

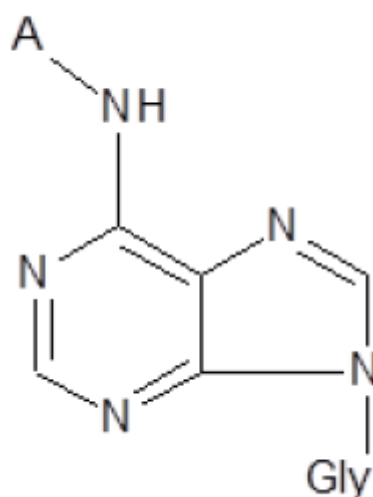
	AGI code	Description	logFC	
			6h	48h
	AT2G47040	Pectin methylesterase Vanguard1 (VGD1)	2.80	5.89
25	AT2G47050	Plant invertase/pectin methylesterase inhibitor superfamily protein	2.31	5.82
	AT3G07820	Pectin lyase-like superfamily protein	2.22	6.45
	AT4G35010	Beta-galactosidase 11 (BGAL11)	2.03	5.33
	AT3G05610	Pectinesterase/pectinesterase inhibitor 21 (PME21)	1.80	5.58
	AT5G44430	Defensin-like protein 1.2C (PDF1.2C)	1.75	8.87
30	AT1G55560	SKU5 similar 14 (SKS14)	1.71	8.75
	AT1G02790	Polygalacturonase 4 (PGA4)	1.67	8.59
	AT5G44420	Defensin-like protein 1.2A (PDF1.2A)	1.58	8.15
	AT2G26020	Defensin-like protein 1.2B (PDF1.2B)	1.52	6.04
	AT2G26010	Defensin-like protein 1.3 (PDF1.3)	1.47	8.23

	AT5G45880	Pollen Ole e 1 allergen and extensin family protein	1.45	5.52
	AT3G62710	Glycosyl hydrolase family protein	1.35	5.26
	AT5G12960	Putative glycosyl hydrolase	1.33	5.26
	AT1G05580	Cation/H(+) exchanger 23 (CHX23)	1.26	5.46
5	AT2G04460	Transposable element gene	1.16	5.43
	AT5G61160	Agmatine coumaroyltransferase (ACT)	1.13	5.05
	AT1G59950	NAD(P)-linked oxidoreductase superfamily protein	1.08	5.72
	AT1G75830	Defensin-like protein 1.1 (PDF1.1)	1.06	7.85
	AT3G28153	Transposable element gene	0.92	5.70
10	AT2G28210	Alpha carbonic anhydrase 2 (ATACA2)	0.85	5.86
	AT3G13400	SKU5 similar 13 (SKS13)	0.82	5.57
	AT4G01390	TRAF-like family protein	0.79	6.24
	AT1G76640	Calcium-binding EF-hand family protein (CML39)	0.78	7.06
	AT2G18150	Peroxidase 15 (PER15)	0.68	7.22
15	AT4G24350	Phosphorylase superfamily protein	0.64	6.45
	AT1G19670	Chlorophyllase-1 (CLH1)	0.63	6.42
	AT3G28155	ARM repeat superfamily protein	0.59	6.06
	AT1G15540	2-oxoglutarate and Fe(II)-dependent oxygenase superfamily protein	0.57	5.63
	AT5G52670	Copper transport family protein	0.57	6.03
20	AT5G63270	RPM1-interacting protein 4 (RIN4) family protein	0.56	7.11
	AT2G39030	L-ornithine N5-acetyltransferase (NATA1)	0.56	5.48
	AT4G21830	Peptide methionine sulfoxide reductase B7 (MSRB7)	0.55	5.95
	AT3G09340	Transmembrane amino acid transporter family protein	0.55	8.54
	AT2G02010	Glutamate decarboxylase 4 (GAD4)	0.55	5.09
25	AT2G21900	WRKY transcription factor 59 (WRKY59)	0.54	5.81
	AT4G26010	Peroxidase 44 (PER44)	0.53	7.92
	AT3G11340	UDP-Glycosyltransferase superfamily protein	0.51	6.60
	AT2G26695	Ran BP2/NZF zinc finger-like superfamily protein	0.50	5.90
	AT1G59860	17.6 kDa class I heat shock protein 1 (HSP17.6A)	0.48	5.47
30	AT4G22620	SAUR-like auxin-responsive family protein	0.46	5.05
	AT4G39320	Microtubule-associated protein-related	0.45	5.09
	AT5G62720	Integral membrane HPP family protein	0.44	5.31
	AT2G37430	Zinc finger protein ZAT11	0.42	4.96
	AT5G03610	GDSL esterase/lipase	0.42	4.61
35	AT4G37780	Myb domain protein 87 (MYB87)	0.41	6.88
	AT4G22030	F-box domain, cyclin-like, F-box domain, Skp2-like protein	0.41	5.02
	AT1G10585	Basic helix-loop-helix (bHLH) DNA-binding superfamily protein	0.38	4.85
	AT3G44830	Putative phospholipid:diacylglycerol acyltransferase 2 (PDAT2)	0.38	4.91
	AT4G31950	Cytochrome P450 82C3 (CYP82C3)	0.37	5.29

CLAIMS

1. 6-aryl-9-glycosidpurine of general formula **Ia**

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**Ia**

and pharmaceutically acceptable salts thereof with alkali metals, ammonia, amines, or
 10 addition salts with acids, wherein

Gly represents β -D-arabinofuranosyl,

A represents benzyl or furfuryl, each of which is substituted by one or more, preferably
 one to three, substituents selected from the group comprising hydroxyl, halogen, alkoxy,
 amino, mercapto, carboxyl, cyano, amido, sulfo, sulfamido, acyl, acylamino, acyloxy,
 15 alkylamino, dialkylamino, alkylmercapto, trifluoromethyl, trifluoromethoxy, or
 unsubstituted furfuryl,

or

Gly represents β -D-2'-deoxyribofuranosyl,

A represents

20 - benzyl which is substituted by one or more, preferably one to three, substituents selected
 from the group comprising amino, mercapto, carboxyl, cyano, amido, sulfo, sulfamido,
 acyl, acylamino, acyloxy, alkylamino, dialkylamino, alkylmercapto, trifluoromethyl,
 trifluoromethoxy, or

- furfuryl which is substituted by one or more, preferably one to three, substituents selected from the group comprising hydroxyl, halogen, alkoxy, amino, mercapto, carboxyl, cyano, amido, sulfo, sulfamido, acyl, acylamino, acyloxy, alkylamino, dialkylamino, alkylmercapto, trifluoromethyl, trifluoromethoxy, or unsubstituted furfuryl.

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2. 6-aryl-9-glycosidpurine according to claim 1, selected from the group comprising 6-(3-fluorofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(4-fluorofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(5-fluorofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3-chlorofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(4-chlorofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(5-chlorofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3-bromofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(4-bromofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(5-bromofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3-hydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(4-hydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(5-hydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(4-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(5-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2-aminofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3-aminofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(4-aminofurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3,5-dihydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,4-dihydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,5-dihydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,6-dihydroxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3,4-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3,5-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,3-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,4-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,5-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2,6-dimethoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2-hydroxy-3-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2-hydroxy-4-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2-hydroxy-5-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(2-hydroxy-6-methoxyfurfurylamino)-9-β-D-arabinofuranosylpurine, 6-(3-hydroxy-2-methoxyfurfurylamino)-9-β-D-

	arabinofuranosylpurine,	6-(3-hydroxy-4-methoxyfurfurylamino)-9-β-D-
	arabinofuranosylpurine,	6-(3-hydroxy-5-methoxyfurfurylamino)-9-β-D-
	arabinofuranosylpurine,	6-(3-hydroxy-6-methoxyfurfurylamino)-9-β-D-
	arabinofuranosylpurine,	6-(4-hydroxy-2-methoxyfurfurylamino)-9-β-D-
5	arabinofuranosylpurine,	6-(4-hydroxy-3-methoxyfurfurylamino)-9-β-D-
	arabinofuranosylpurine,	6-(4-hydroxy-5-methoxyfurfurylamino)-9-β-D-
	arabinofuranosylpurine,	6-(4-hydroxy-6-methoxyfurfurylamino)-9-β-D-
	arabinofuranosylpurine, 6-(2-fluorobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-fluorobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-fluorobenzylamino)-9-β-D-
10	arabinofuranosylpurine, 6-(2-bromobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-bromobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-bromobenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(2-iodobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-iodobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-iodobenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(2-chlorobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-chlorobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-chlorobenzylamino)-9-β-D-
15	chlorobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-chlorobenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(4-chlorobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-methoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-methoxybenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(4-methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-hydroxybenzylamino)-9-β-D-
20	arabinofuranosylpurine, 6-(4-hydroxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-fluoro-6-(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(3-chloro-2,6-
	difluorobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-
	(trifluoromethylthio)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-chloro-3,6-
	difluorobenzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-
25	(trifluoromethylthio)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-fluoro-5-
	(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-chloro-4-
	fluorobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-(trifluoromethoxy)benzylamino)-	9-β-D-arabinofuranosylpurine,
	arabinofuranosylpurine,	6-(3-(trifluoromethyl)benzylamino)-9-β-D-
	arabinofuranosylpurine,	6-(2-(trifluoromethyl)benzylamino)-9-β-D-
30	arabinofuranosylpurine,	6-(4-(trifluoromethyl)benzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(4-chloro-3-	
	(trifluoromethyl) benzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-fluoro-3-
	(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(3,5-

	bis(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-
	(trifluoromethoxy)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-
	(trifluoromethoxy)benzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-
	(trifluoromethyl)benzylamino)-9-β-D-arabinofuranosylpurine, 6-(2-aminobenzylamino)-9-	
5	β-D-arabinofuranosylpurine, 6-(3-aminobenzylamino)-9-β-D-arabinofuranosylpurine, 6-	
	(4-aminobenzylamino)-9-β-D-arabinofuranosylpurine, 6-(4-diethylaminobenzylamino)-9-	
	β-D-arabinofuranosylpurine,	6-(3,4-dihydroxybenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(3,5-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-	
	(3,4-dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2,4-
10	dihydroxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,5-dihydroxybenzylamino)-9-	
	β-D-arabinofuranosylpurine,	6-(2,6-dihydroxybenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(3,4-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-	
	(3,4-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3,5-
	dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,3-dimethoxybenzylamino)-9-	
15	β-D-arabinofuranosylpurine,	6-(2,4-dimethoxybenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(2,5-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-	
	(2,6-dimethoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxy-3-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxy-4-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxy-5-
20	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxy-6-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-hydroxy-2-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-hydroxy-4-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-hydroxy-5-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(3-hydroxy-6-
25	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-hydroxy-2-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-hydroxy-3-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-hydroxy-5-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(4-hydroxy-6-
	methoxybenzylamino)-9-β-D-arabinofuranosylpurine, 6-(2,3,4-trimethoxybenzylamino)-	
30	9-β-D-arabinofuranosylpurine,	6-(2,4,5-trimethoxybenzylamino)-9-β-D-
	arabinofuranosylpurine, 6-(2,4,6-trimethoxybenzylamino)-9-β-D-arabinofuranosylpurine,	
	6-(3,4,5-trimethoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxy-3,4,5-
	trimethoxybenzylamino)-9-β-D-arabinofuranosylpurine,	6-(2-hydroxy-3,4,6-

- trimethoxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-4,5,6-trimethoxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2,4,6-trimethoxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2,3,4-trihydroxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2,4,6-trihydroxybenzylamino)-9- β -D-arabinofuranosylpurine,
- 5 6-(2,3,4-trihydroxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(3,4,5-trihydroxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2,4,6-trihydroxybenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-3-chlorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-4-chlorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-5-chlorobenzylamino)-9- β -D-
- 10 arabinofuranosylpurine, 6-(2-hydroxy-6-chlorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-3-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-4-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-5-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-6-iodobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-3-bromobenzylamino)-9- β -D-
- 15 arabinofuranosylpurine, 6-(2-hydroxy-4-bromobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-5-bromobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-6-bromobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-3-fluorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(2-hydroxy-4-fluorobenzylamino)-9- β -D-
- 20 arabinofuranosylpurine, 6-(2-hydroxy-5-fluorobenzylamino)-9- β -D-arabinofuranosylpurine, 6-(3-fluorofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-fluorofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(5-fluorofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-chlorofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-chlorofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine,
- 25 6-(5-chlorofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-bromofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-bromofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(5-bromofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-hydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-hydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(5-hydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine,
- 30 9- β -D-2'-deoxyribofuranosylpurine, 6-(3-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(5-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2-aminofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine,

- 6-(3-aminofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-aminofurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3,5-dihydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3,4-dihydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,4-dihydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,5-dihydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,6-dihydroxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3,4-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3,4-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3,5-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,3-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,4-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,5-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2,6-dimethoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2-hydroxy-3-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2-hydroxy-4-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2-hydroxy-5-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2-hydroxy-6-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-hydroxy-2-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-hydroxy-4-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-hydroxy-5-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-hydroxy-6-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-hydroxy-2-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-hydroxy-3-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-hydroxy-5-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-hydroxy-6-methoxyfurfurylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(2-aminobenzylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(3-aminobenzylamino)-9- β -D-2'-deoxyribofuranosylpurine, 6-(4-aminobenzylamino)-9- β -D-2'-deoxyribofuranosylpurine.

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3. Cosmetic compositions containing as an active ingredient at least one compound of general formula **Ia** according to claim 1 or 2.