

Novel Alkyl Phospholipid Derivatives with reduced Cytotoxicity and Uses thereofDescription5 Technical field

The invention relates to novel alkyl phospholipid derivatives with reduced cytotoxicity that are useful in the treatment of various diseases and/or pathophysiological conditions in mammals caused by microorganisms, in particular
10 bacteria, fungi, protozoa, and/or viruses. Such alkyl phospholipids can be employed as single drugs or in combination therapies and may also exhibit anti-neoplastic properties.

Prior art

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Alkyl phospholipids (APL) as a substance class have been known for several decades to possess properties and exhibit biological activity that can advantageously be exploited for treatment in various medicinal indications.

A comprehensive overview of different effects and uses of for instance alkyl
20 phosphocholines is given in Drugs of Today, Vol. 34, Suppl. F, 1998.

Further literature with regard to alkyl phospholipids, their various uses as well as relevant indications (including respective standard therapies) comprise the following.

EP 0 108 565 discloses alkyl phosphocholines that are claimed to possess anti-
25 neoplastic properties. WO 87/03478 describes alkyl phospholipids for use as anti-tumor medicaments. US 5,219,866 describes octadecyl-[2-(N-methylpiperidino)-ethyl]-phosphate as useful for the treatment of cancer as well as a process for its preparation. US 6,172,050, US 6,479,472 and EP 0 579 939 all disclose specific phospholipid derivatives and methods of using them as therapeutics, in particular against tumors.
30 US 5,449,798 and US 5,958,906 are directed to phospholipid derivatives containing higher elements of the fifth group that are said to act as anti-neoplastic. US 6,093,704 describes the use of dopamine receptor antagonists in palliative tumor therapy reducing potential side effects of alkyl phosphocholines, such as miltefosine. WO 2004/012744 relates to the use of alkyl phosphocholines in combination with

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antitumor medicaments.

- EP 0 108 565 discloses alkyl phosphocholines that are claimed among others to have anti-fungal properties. Lu et al. describe the use of the natural bisphosphocholine 5 irlbacholine and synthetic analogues thereof as antifungal agents (Lu Q et al., J. Nat. Prod. 1999, 62(6):824-828). Ganendren and co-workers studied for compounds with structural similarities to phospholipid substrates as inhibitors of phospholipases from the fungal pathogen *Cryptococcus neoformans* (Ganendren R et al., Antimicrob. Agents Chemother. 2004, 48(5):1561-1569).
- 10 Koufaki M et al. describe alkyl and alkoxyethyl phospholipids as antineoplastics for the treatment of tumors (Koufaki et al., J. Med. Chem. 1996, 39:2609-2614). Konstatinov et al. elucidate the apoptotic mode of action of selected alkylphospholipids (Konstatinov et al., Cancer Chemother. Pharmacol. 1998, 41:210-216). Engel et al. discuss the pharmacological activity of perifosine as an anti-tumor medicament (Engel 15 et al., Drugs of the Future 2000, 25(12):1257-1260). WO 00/33917 discloses agents based on liposomes that may contain miltefosine or perifosine and may be used for treating tumors. EP 0 284 395 describes novel glycerol derivatives and anti-hypertensive agents for reducing blood pressure. Andresen and co-workers studied the biological activity of synthesized anticancer ether lipids that are specifically released by 20 phospholipase A2 in tumor tissue (Andresen TL et al., J. Med. Chem. 2005, 48:7305-7314).

- Protozoal diseases persist to be a worldwide burden. For most of these diseases curing therapies are not available. Leishmaniasis and Chagas disease are two 25 prominent members of this class of diseases.

- Leishmaniasis ranks third in the WHO neglected diseases list in terms of fatality numbers per year. With annually 60.000 cases of death only Malaria and tuberculosis cause more victims. It is estimated that worldwide 350 million people are at risk and currently 12 million people are infected. The disease is found in 88 countries of the new 30 and old world with most infected people living in India, Bangladesh, Brazil and Sudan. Each year, 1-1.5 million new cases are reported. The DALY burden has been reported by WHO/TDR to be 860.000 for men and 1.200.000 for women.

Leishmaniasis is caused by protozoa of the genus *Leishmania* which are

transmitted by sand flies (*Phlebotomus* sp. and *Lutzomyia* sp.). Two forms of the disease exist. Internal or visceral leishmaniasis is the most dangerous form and causes death within 6-12 month if untreated. The other form, called cutaneous leishmaniasis, leads to lesions in the skin and if untreated to ulcers. In cases where no spontaneous healing occurs it results in scars on body and face. Possible complications of untreated leishmaniasis comprise secondary infections of ulcer and development of the mucocutaneous form which can result in destruction of facial skin and mucosal parts.

The visceral form is found in the old (*Leishmania* species: *L. donovani*, *L. infantum*) and new (*L. chagasi*) world. It affects the subindian continent (India, Bangladesh and Nepal), parts of East Africa (Sudan and Ethiopia) and parts of South America (Brazil and Colombia). The number of new cases per year is 500.000 with a high rate of mortality. Visceral leishmaniasis is associated with fever, weight loss, enlargement of spleen and liver. If it is not treated it tends to be fatal.

The cutaneous form is widespread in both worlds. In the old world, *Leishmania major* and *Leishmania tropica* are the prominent pathogens. *L. major* is found in rural areas whereas *L. tropica* is found in urban areas. The main countries are Afghanistan, Pakistan and the whole Middle East, especially Iran, Iraq, Syria and Saudi-Arabia.

Currently, there is a tendency to leave the patients untreated because scars and painful ulcers are considered as non-life threatening. However, it is more likely to be the high risk of side effects caused by current treatment that could explain the wait-and-see position. In the new world the situation is more dangerous. Patients suffering from cutaneous leishmaniasis may develop the mucocutaneous form which leads to painful and disfiguring disruption of parts of the face. The disease is found all over Middle and South America with focal points in Venezuela, Peru, Bolivia and Guatemala.

The current standard therapy has to be given parenterally in hospitals and is highly toxic. AIDS and other immunosuppressive conditions such as malnutrition increase the risk. As a matter of fact, in many of the countries where visceral Leishmaniasis prevails they are also hot spots for AIDS and malnutrition. The current treatment options are limited. Since 50 years parenteral antimonials (sodium stibogluconate, SSG, Pentostam™ and meglumine stibogluconate Glucantime™) have been the standard therapy for Leishmaniasis. The side effects are very serious including vomiting, nausea, diarrhoea and anorexia. Creatine values have to be observed and ECG values have to be monitored during the whole course of treatment and a regular ECG

monitoring is required.

The alternative and second line treatment amphotericin B has its advantage in the absence of resistance. However, in addition to the high cost for hospitalization there is a higher drug price. Side effects are similarly serious with additional drug-induced
5 fevers and the drug is only approved for visceral leishmaniasis. A further alternative to overcome side effects is the use of liposomal amphotericin B. The drug paromomycin currently undergoes clinical phase III trials and it is reported that it is efficient in 95% of the cases and generally well tolerable. All treatments are parenteral and require a longer period of hospitalization.

10 Compared to Leishmaniasis, for Chagas disease the situation is much more problematic. Chagas disease, also called American trypanosomiasis, is caused by the parasite protozoon *Trypanosoma cruzi*. It is endemic in 21 countries of South and Latin America. Currently 16-18 million people are infected and 100 million people are at risk. The disease is transmitted via blood-sucking insects the parasites being transmitted
15 from the gastric-enteral path while the insect is incorporating blood of its victim.

In human the disease starts with an acute phase followed by a life-long chronic phase. In the acute phase it is sometimes associated with fever, swelling of lymph glands, enlargement of the liver and spleen as well as local inflammations. Because the acute phase is often not correctly if at all diagnosed, the infection stays untreated.
20 As a consequence, Chagas disease enters the chronic phase which is characterized by the parasite's penetration of the heart muscle, severe local inflammation and chronic heart disease. Usually, patients die early on because of these cardiac diseases.

[General literature on Chagas Disease: Guzman-Bracho C, Trends Parasitol. 2001, 17(8):372-376; Roberts A et al., J. Am. Acad. Nurse Pract. 2001, 13(4):152-153;
25 Tarleton RL et al., Parasitol. Today. 1999, 15(3):94-99; Anez N et al., Mem. Inst. Oswaldo Cruz 2004, Rio de Janeiro, 99(8): 781-787; Second Report of the WHO Expert Committee, WHO technical report series 905, WHO 2002; Behbehani K, Bull World Health Organ. 1998, 76 (Suppl. 2):64-67; Umezawa ES et al., Lancet. 2001, 357(9258):797-799].

30 So far the treatment options have been limited. There are only two drugs approved for Chagas disease: Benznidazole (Radanil™) and Nifurtimox (Lampit™). They are very toxic and their use is limited to the acute phase of the disease only. Only poor evidence has been reported that at least one of the two drugs is of some efficiency in the chronic phase.

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Currently, the drug of choice is Benznidazole which is given at 5-7 mg per kg bodyweight for 60 days. Side effect can be very severe and request an immediate notification to the physician. Very common side effects reported are convulsions (seizures), numbness, tingling pain, weakness in hands or feet, reddish discoloration of skin, abdominal or stomach pain, diarrhoea, nausea and vomiting. Rare side effects are fever or chills, pinpoint red spots on skin, skin rash, sore throat, unusual bleeding or bruising, confusion, dizziness, headache, restlessness, temporary loss of memory, trouble in sleeping, difficulty in concentrating, unusual tiredness or weakness.

The older substance Nifurtimox is much less in use than Benznidazole. It has to be given for 50 days at 8-10 mg per kg bodyweight. Known side effects are abdominal or stomach pain, dizziness, headache, loss of appetite, nausea, vomiting, weight loss, skin rash, chills or sore throat, clumsiness or unsteadiness, confusion, convulsions (seizures), decreased sexual drive or ability, fever, forgetfulness, irritability, mood or mental changes, muscle weakness, numbness, tingling, pain, weakness in hands or feet, trembling, trouble in sleeping, uncontrolled back-and-forth and/or rolling eye movements, unusual excitement, nervousness and restlessness.

[Literature on Chagas disease (standard) treatment: Coura JR et al., Mem. Inst. Oswaldo. Cruz 2002, Rio de Janeiro, 97(1): 3-24; Docampo R, Curr. Pharm. Des. 2001, 7(12):1157-1164; Kayser O et al., Pharm. Unserer Zeit. 1999, 28(4):177-185; Cerecetto H et al., Curr. Top. Med. Chem. 2002, 2(11):1187-1213; Urbina JA, Curr. Opin. Infect. Dis. 2001, 14(6):733-741; Paulino M et al., Mini-Reviews in Medicinal Chemistry 2005, 5: 499-519; Campos RF et al., Rev. Soc. Bras. Med. Trop. 2005, 38(2):142-146; Garcia S et al., Antimicrob. Agents Chemother. 2005, 49(4):1521-1528; Schenone H et al., Rev. Méd. Chile 2003; 131:1089-1090; Marcondes MC et al., Microbes Infect. 2000, 2(4):347-352; Corrales M et al., Antimicrob. Agents Chemother. 2005, 49(4):1556-1560; Urbina JA et al., Int. J. Antimicrob. Agents 2003, 21(1):39-48; Maya JD et al., Biochem. Pharmacol. 2003, 65(6):999-1006; Lockman JW et al., Curr. Med. Chem. 2005, 12(8):945-959].

The use of alkyl phospholipids in protozoal diseases, in particular Leishmaniasis and Chagas disease has also been reported. Miltefosine has been shown to be as high effective in the treatment of Leishmaniasis as currently used amphotericin B. It has been registered as the first oral drug in several countries for cutaneous and visceral leishmaniasis. However, there is still a need to improve therapy schemes and efficacy

in the course of Leishmaniasis treatment. There is an increasing danger that due to the long metabolic half-life period of the drug and the long lasting therapy course of 28 days – which may not be completely followed by the patients – development of drug resistance will occur. Alkyl phospholipids have also been shown in preclinical test to be
 5 active in acute phase *in vivo* and *in vitro* against *Trypanosoma cruzi*.

[Literature on use of APL in Leishmaniasis and Chagas disease: Croft SL et al., Mol. Biochem. Parasitol. 2003, 126(2):165-172; Saraiva VB et al., Antimicrob. Agents Chemother. 2002, 46(11):3472-3477; de Castro SL et al., Mini-Reviews in Medicinal Chemistry 2004, 4:141-151; Berman J, Expert Opin. Pharmacother. 2005, 6(8):1381-
 10 1388; Bhattacharya SK et al., Clin. Infect. Dis. 2004, 38(2):217-221; Jha TK et al., N. Engl. J. Med. 1999, 341(24):1795-1800; Jacobs S, N. Engl. J. Med. 2002, 347(22):1737-1738; Sundar S et al., N. Engl. J. Med. 2002, 347(22):1739-1746; Sindermann H et al., Clin. Infect. Dis. 2004, 39(10):1520-1523; Soto J et al., Clin. Infect. Dis. 2004, 38(9):1266-1272; Soto J et al., Clin. Infect. Dis. 2001, 33(7):E57-61;
 15 Sundar S et al., Pediatr. Infect. Dis. J. 2003, 22(5):434-438; Croft SL et al., J. Antimicrob. Chemother. 1996, 38(6):1041-1047; Santa-Rita RM et al., Acta Trop. 2000, 75(2):219-228; Sundar S et al., Lancet. 1998, 352 (9143): 1821-1823; Sundar S et al., Ann. Trop. Med. Parasitol. 1999, 93(6):589-597; Sundar S et al., Clin. Infect. Dis. 2000, 31(4):1110-1113; Lux H et al., Mol. Biochem. Parasitol. 2000, 111(1):1-14;
 20 US 5,980,915, US 6,521,879, US 6,506,393; US 2003/0216355; US 2004/0242543; Verma NK et al., Antimicrob. Agents Chemother. 2004, 48(8):3010-3015; Walochnik J et al., Antimicrob. Agents Chemother. 2002, 46(3):695-701; Seifert K et al., Antimicrob. Agents Chemother. 2006, 50(1):73-79].

25 As for protozoal diseases, in particular Leishmaniasis and Chagas disease, combination therapy approaches have only been rarely reported. The efficacy of picroliv in combination with miltefosine was described by Gupta and co-workers (Gupta S et al., Acta Trop. 2005, 94(1):41-47). A potential anti-proliferative synergy of lysophospholipid analogues and ketoconazole against *Trypanosoma cruzi* was
 30 discussed by Santa-Rita and collaborators (Santa-Rita RM et al., J. Antimicrob. Chemother. 2005, 55(5):780-784). Mechanism of action of anti-proliferative lysophospholipid analogues against the protozoan parasite *Trypanosoma cruzi* were elucidated by Lira et al. who postulated a potentiation of *in vitro* activity by the sterol biosynthesis inhibitor ketoconazole (Lira R et al., J. Antimicrob. Chemother. 2001,

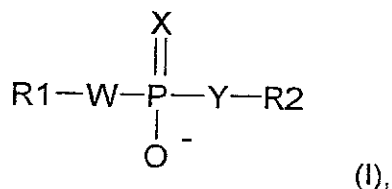
47(5):537-546). Araujo and co-workers showed that a combination of benznidazole and ketoconazole enhances efficacy of chemotherapy of experimental Chagas disease (Araujo MS et al., J. Antimicrob. Chemother. 2000, 45(6):819-824).

5 Kanetani/Kanaya F et al. describe the synthesis, physicochemical properties and antimicrobial properties of long chain alkylphosphorylcholines. The authors show that the compounds studied exhibit virtually no antibacterial properties against *Escherichia coli* and *Staphylococcus aureus*. However, two of them exhibit an antifungal effect against *Aspergillus oryzae* (Kanetani/Kanaya F et al., *Nippon Kagaku Zasshi* 1984, 9:1452-1458). Berger and co-workers studied the influence of
10 dodecylphosphocholine on tumor regression and virus-infected cells (Berger MR et al., *J. Cancer Res. Clin. Oncol.* 1993, 119:541-548). Ng et al. investigated the correlation of antifungal activity with fungal phospholipase inhibition using a series of bisquaternary ammonium salts (Ng et al., *J. Med. Chem* 2006, 49:811-816). Widmer et al. describe the fungicidal activity of hexadecylphosphocholine in a mouse model of
15 cryptococcosis (Widmer F et al., *Antimicrob. Agents Chemother.* 2006, 50(2):414-421).

However, alkyl phospholipid derivatives known in the prior art and uses thereof do show inherent disadvantages. In particular, standard drug medication (APL and others) against bacterial, fungal, protozoal and/or viral diseases implicate several
20 drawbacks, such as resistance of the microorganisms to be targeted, severe side effects caused by the high toxicity of the compounds to be applied and long courses of treatment.

Summary

In one aspect, there is provided the use of an alkyl phospholipid derivative according to formula (I)



wherein:

W, X, Y independently are selected from the group consisting of: "oxygen atom, sulphur atom";

R1 is -R5;

R2 is -R8;

R5 is independently selected from the group consisting of: substituted or unsubstituted C8-C30 "alkyl" ", where "alkyl" stands for acyclic and cyclic saturated, unsaturated or partially unsaturated hydrocarbons which may be straight chain, branched or cyclic, and cyclic hydrocarbons as part of a straight-chain or branched hydrocarbon system and which may contain one or more double and/or triple bonds;

R8 is selected from the group consisting of: "substituted or unsubstituted heterocycle", where heterocycle is

- (i) a 5-, 6- or 7-membered saturated, partially unsaturated or aromatic monocyclic carbon atom ring system with at least one heteroatom selected from the group consisting of: "nitrogen atom, oxygen atom, sulphur atom, arsenic atom", and with the proviso that at least one heteroatom is a quaternary nitrogen atom or a quaternary arsenic atom,

where two or more ring atoms of heterocycle can be additionally linked via an alkylene-bridge, and where heterocycle if substituted is substituted with at least one radical R12, which in case of two or more radicals R12 are independently from each other identical, partly identical or different;

R12 is independently from each other selected from the group consisting of: "hydrogen atom, substituted or unsubstituted C1-C18 "alkyl", substituted or unsubstituted "C3-C8 cycloalkyl", substituted or unsubstituted (C1-C12 "alkyl")_s-B-(C1-C12 "alkyl")_t-D-(C1-C12"alkyl")_u, substituted or unsubstituted "aryl", substituted or unsubstituted "heteroaryl", substituted or unsubstituted "alkoxy", -OH, halogen, -F, -Cl, -Br, -I, =O, -C(O)O-(C1-C12 "alkyl"), -C(O)O-(C3-C8 cycloalkyl), -C(O)O-"aryl", -C(O)O-"heteroaryl", -C(O)O-"heterocyclyl", -C(O)-(C1-C12 "alkyl"), -C(O)-(C3-C8 "cycloalkyl"), -C(O)-"aryl", -C(O)-"heteroaryl", -C(O)-"heterocyclyl" ", and

optionally two substituents R12 can together form a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms;

where "alkyl" has the meaning defined above; "C3-C8 cycloalkyl" stands for a saturated or partially unsaturated non-aromatic cyclic hydrocarbon group containing 3 to 8 carbon atoms that may optionally be linked via an "alkyl" group, in which the "alkyl" group has the meaning defined above; "aryl" stands for aromatic systems having 3 to 14 carbon atoms, including systems in which the aromatic cycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system; "heteroaryl" stands for a 5-, 6- or 7-membered cyclic aromatic radical which comprises at least 1 heteroatom; "alkoxy" stands for radicals in which an "alkyl" group as defined above, a "C3-C8 cycloalkyl" as defined above, an "aryl" group as defined above, a "heteroaryl" group as defined above and/or a "heterocyclyl" group is linked via an oxygen atom, in which the "heterocyclyl" group stands for a mono- or polycyclic system of 3 to 20 ring atoms which may be unsaturated, mono- or poly unsaturated but may not be aromatic;

B, D are independently from each other selected from the group consisting of "oxygen atom; sulphur atom; S(O₂)";

s, t, u independently from each other are 0 or 1;

for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals selected from the group consisting of aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, dermatomycosis, dermatophytosis, histoplasmosis, lobomycosis, mucormycosis, mycetoma, mycotic keratitis, oculomycosis, onychomycosis, otomycosis, paracoccidiomycosis, phaeohyphomycosis, piedra, pityriasis versicolor, rhinosporidiosis, sporotrichosis, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea favosa, tinea nigra, tinea pedis, tinea unguium, zygomycosis.

Description of the invention

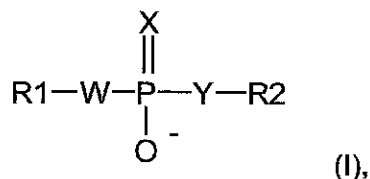
The present invention has the object to provide novel alkyl phospholipid derivatives which can be employed for the treatment of diseases or pathophysiological conditions in mammals caused by microorganisms, in particular bacteria, fungi, protozoa and/or viruses. It is another object of the underlying invention to provide novel alkyl phospholipid derivatives that exhibit anti-neoplastic properties and can be used for treating tumors in mammals. A further object of the present invention is to provide novel combination therapies of alkyl phospholipid derivatives with suitable known drugs for the treatment of diseases or pathophysiological conditions in mammals caused by

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microorganisms, in particular protozoa.

The object of the present invention has surprisingly been solved in one aspect by providing alkyl phospholipid derivatives according to formula (I)

5



wherein:

10 W, X, Y independently are selected from the group consisting of: "oxygen atom, sulphur atom";

R1 is " $-\text{[(CR}_3\text{R}_4)_m\text{-Z]}_n\text{-R}_5$ ";

R2 is " $-(\text{CR}_6\text{R}_7)_p\text{-R}_8$ ";

15 R3 and R4 are independently from each other selected from the group consisting of "hydrogen atom; substituted or unsubstituted C1-C12alkyl, substituted or unsubstituted $(\text{C1-C12alkyl})_q\text{-A-(C1-C18alkyl)}_r$, -OH, substituted or unsubstituted $-\text{C(O)}-(\text{C8-C30alkyl})$, substituted or unsubstituted $-\text{OC(O)}-(\text{C8-C30alkyl})$, substituted or unsubstituted $-\text{NHCO}-(\text{C1-C12alkyl})$, substituted or unsubstituted $-\text{N(C1-C12alkyl)CO}-(\text{C1-C12alkyl})$ ";

20 or optionally R3 and R4 together form a substituted or unsubstituted saturated, partially unsaturated or aromatic heterocyclic ring system of 3, 4, 5, 6, 7 or 8 ring atoms containing at least one heteroatom selected from the group consisting of: "oxygen atom, sulfur atom";

25 R5 is independently selected from the group consisting of: "substituted or unsubstituted C8-C30alkyl, substituted or unsubstituted $-\text{C(O)}-(\text{C8-C30alkyl})$, substituted or unsubstituted steroid moiety";

R6 and R7 are independently from each other selected from the group consisting of "hydrogen atom, -OH, halogen atom, -F, -Cl, -Br, -I, -CN, C1-C6alkyl, -CF₃, -N₃, -NH₂, -NO₂, -OCF₃, -SH";

or optionally R6 and R7 together form a substituted or unsubstituted saturated,

partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms;
 or optionally if p is 1, " $-(CR_6R_7)_p-$ " can also be a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms formed together by R6 and R7;

- 5 R8 is selected from the group consisting of: " $-VR_9R_{10}R_{11}$ "; substituted or unsubstituted heterocycle", where heterocycle is
- (i) a 5-, 6- or 7-membered saturated, partially unsaturated or aromatic monocyclic carbon atom ring system with at least one heteroatom selected from the group consisting of: "nitrogen atom, oxygen atom, sulphur atom, arsenic atom", and
 10 with the proviso that at least one heteroatom is a quaternary nitrogen atom or a quaternary arsenic atom, or
 - (ii) a 7-, 8-, 9-, 10-, 11- or 12-membered saturated, partially unsaturated or aromatic bicyclic carbon atom ring system with at least one heteroatom selected from the group consisting of: "nitrogen atom, oxygen atom, sulphur
 15 atom, arsenic atom", and with the proviso that at least one heteroatom is a quaternary nitrogen atom or a quaternary arsenic atom, or
 - (iii) a tropin moiety,

where two or more ring atoms of heterocycle can be additionally linked via an alkylene-bridge, and where heterocycle if substituted is substituted with at least one
 20 radical R12, which in case of two or more radicals R12 are independently from each other identical, partly identical or different;

R9, R10, R11, R12 are independently from each other selected from the group consisting of: "hydrogen atom, substituted or unsubstituted C1-C18alkyl, substituted or unsubstituted C3-C8cycloalkyl, substituted or unsubstituted (C1-C12alkyl)_s-B-(C1-C12alkyl)_t-C-(C1-C12alkyl)_u, substituted or unsubstituted aryl,
 25 substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, -OH, halogen, -F, -Cl, -Br, -I, =O, -C(O)O-(C1-C12alkyl), -C(O)O-(C3-C8cycloalkyl), -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)O-heterocyclyl, -C(O)-(C1-C12alkyl), -C(O)-(C3-C8cycloalkyl), -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl", and
 30 optionally two substituents R12 can together form a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms;

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Z is independently selected from the group consisting of "oxygen atom; sulphur atom";

V is independently selected from the group consisting of "nitrogen atom, arsenic atom";

5 A, B, C are independently from each other selected from the group consisting of "oxygen atom; sulphur atom; S(O₂)";

m independently is 1, 2 or 3;

n independently is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably is 0, 1, 2, or 3;

p independently is 0, 1, 2, 3, 4, 5 or 6, and preferably is 0, 1, 2 or 3;

10 q, r, s, t, u independently from each other are 0 or 1;

that can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

If R1 is " $-(\text{CR}_3\text{R}_4)_m\text{-Z}]_n\text{-R}_5$ " and $n \geq 2$, then for each " $-(\text{CR}_3\text{R}_4)_m\text{-Z}]$ " group Z,
15 R3 and R4 can be identical, partly identical or different, for instance, " $-\text{CH}_2\text{-O-CHCH}_3\text{-S-CH}_2\text{-O-}$ ".

In a preferred embodiment, alkyl phospholipid derivatives according to above formula (I) are provided, where

20 p is 0,

R2 is R8,

R8 is "substituted or unsubstituted heterocycle",

that can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are
25 caused by microorganisms.

In another preferred embodiment, alkyl phospholipid derivatives according to above formula (I) are provided, where

p independently is 1, 2, 3, 4, 5 or 6, and preferably is 2 or 3;

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R8 is "substituted or unsubstituted heterocycle",

that can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

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In yet another preferred embodiment, alkyl phospholipid derivatives according to above formula (I) are provided, where

p independently is 1, 2, 3, 4, 5 or 6, and preferably is 2 or 3;

R8 is "-VR9R10R11",

10 that can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

15 In a further preferred embodiment, alkyl phospholipid derivatives according to above formula (I) are provided, where

R1 is R5,

n is 0,

20 that can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

In another preferred embodiment, alkyl phospholipid derivatives according to above formula (I) are provided, where

m is 2 or 3,

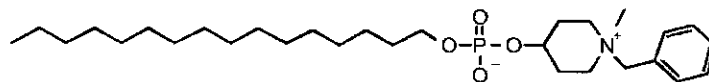
25 n is 1 or 2,

that can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

30 In another aspect, the object of the invention has surprisingly been solved by

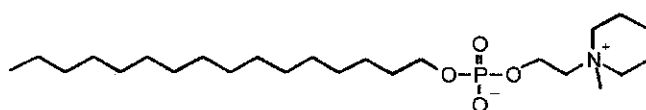
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providing novel alkyl phospholipid derivatives selected from the group consisting of:

“Compound 1

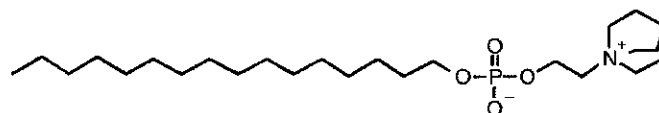
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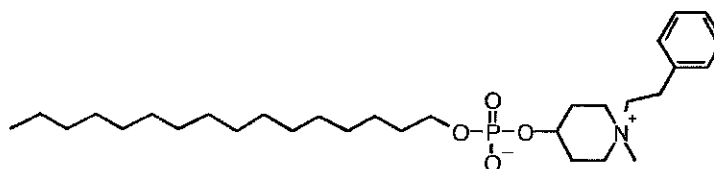
Compound 2

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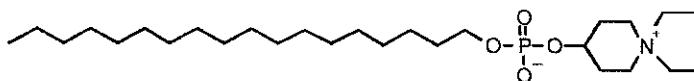
Compound 3

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Compound 4

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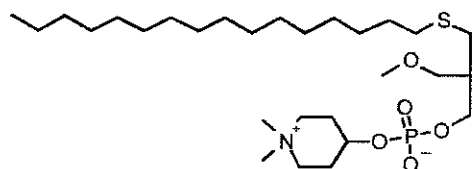
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Compound 5

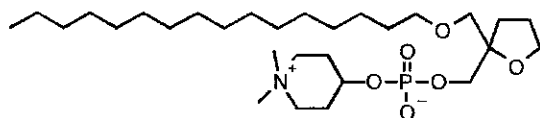
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- 13 -

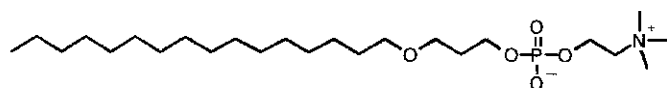
Compound 6

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Compound 7

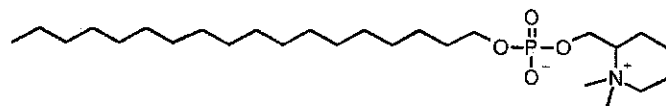
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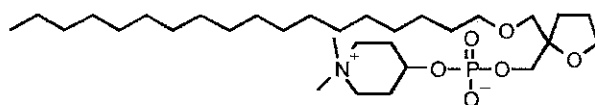
Compound 8

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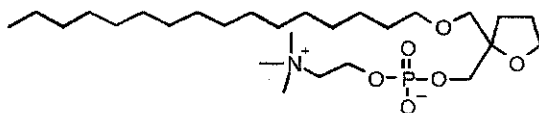
Compound 9

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Compound 10

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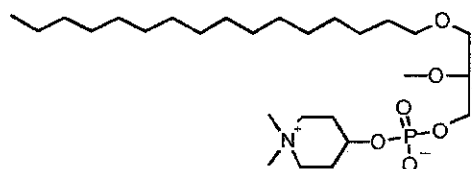
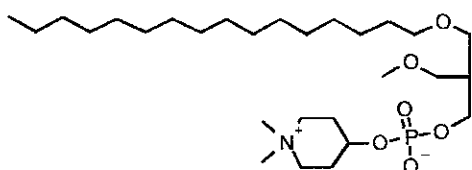
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Compound 11

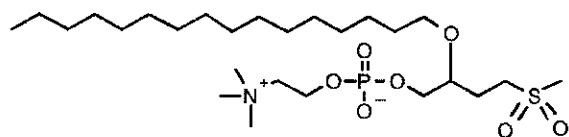
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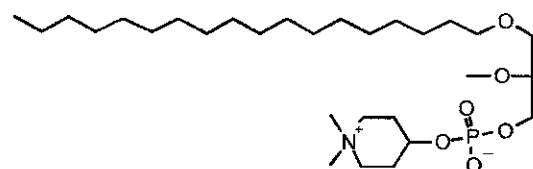
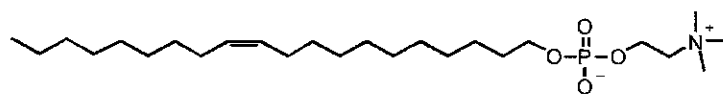
- 14 -

Compound 12**Compound 13**

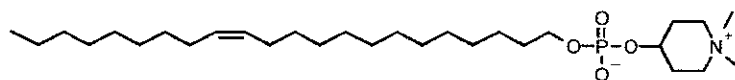
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Compound 14

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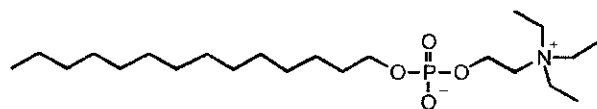
Compound 15**Compound 16**

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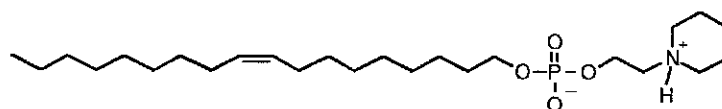
Compound 17

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- 15 -

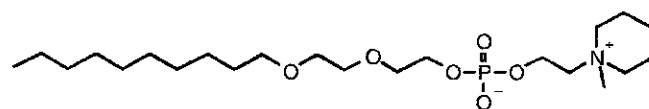
Compound 18

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Compound 19

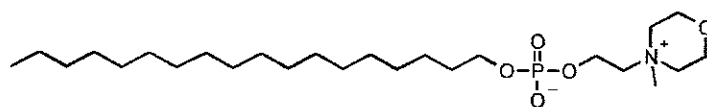
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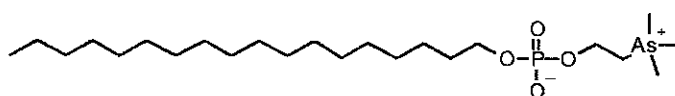
Compound 20

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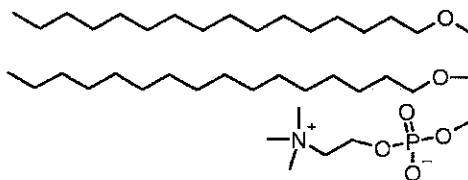
Compound 21

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Compound 22

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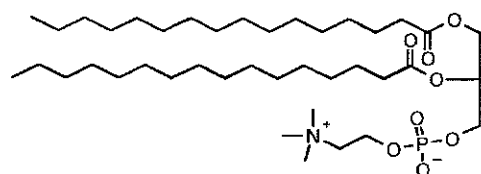
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Compound 23

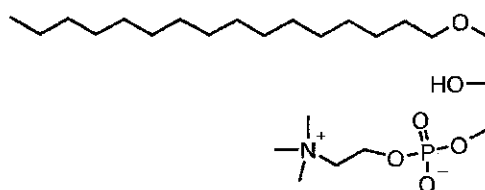
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- 16 -

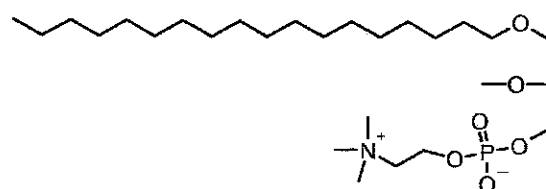
Compound 24

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Compound 25

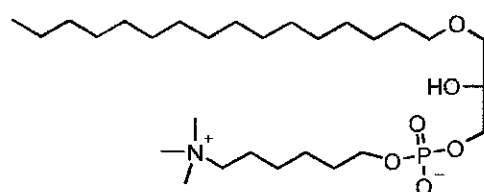
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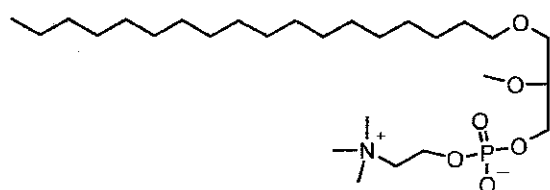
Compound 26

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Compound 27

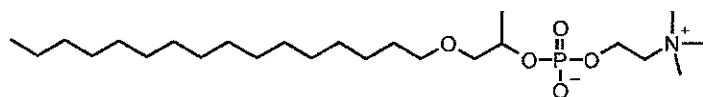
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Compound 28

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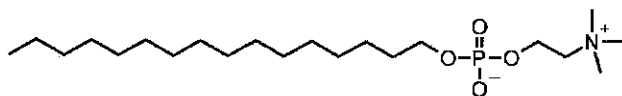
- 17 -

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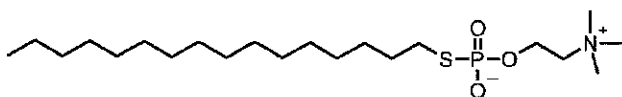
Compound 29

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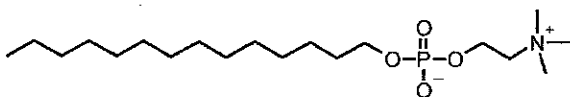
Compound 30

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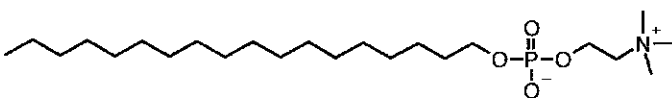
Compound 31

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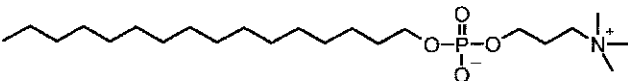
Compound 32

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Compound 33

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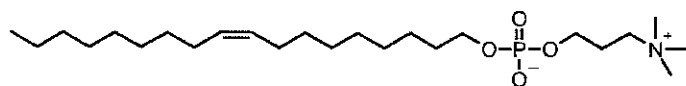
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Compound 34

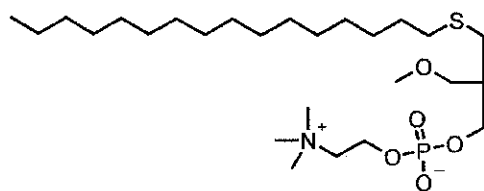
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- 18 -

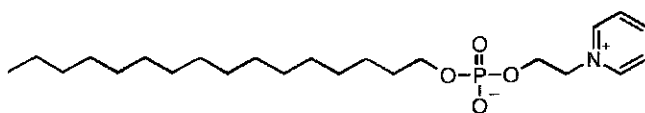
Compound 35

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Compound 36

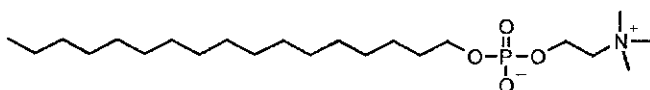
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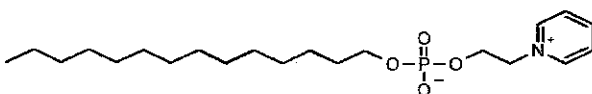
Compound 37

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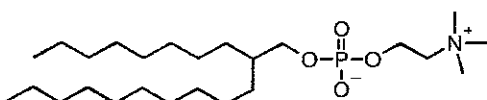
Compound 38

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Compound 39

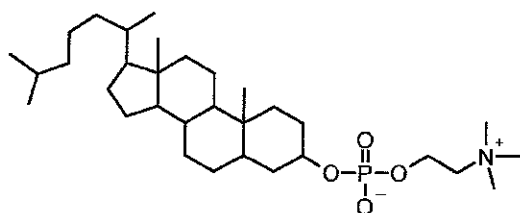
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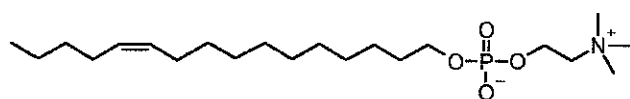
Compound 40

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- 19 -

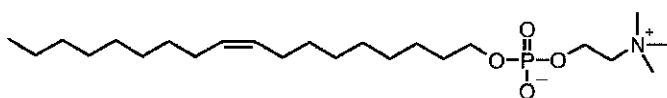
Compound 41

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Compound 42

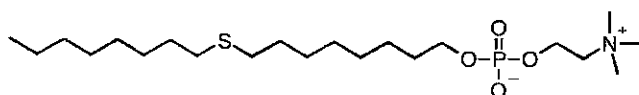
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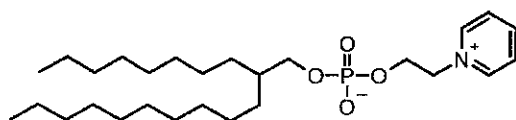
Compound 43

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Compound 44

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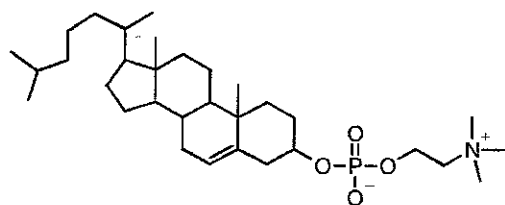
Compound 45

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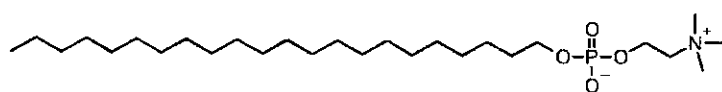
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- 20 -

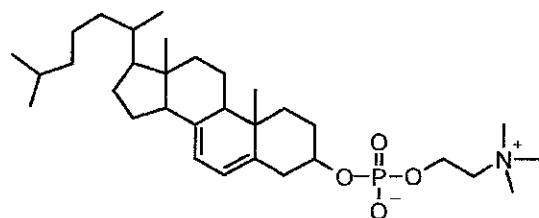
Compound 46

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Compound 47

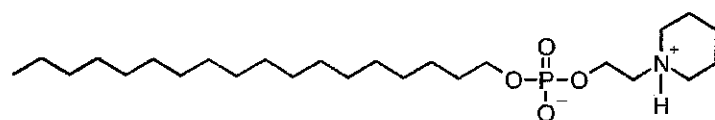
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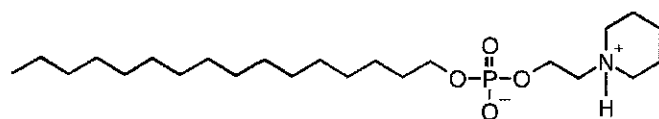
Compound 48

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Compound 49

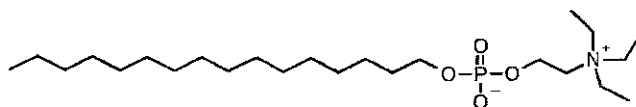
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Compound 50

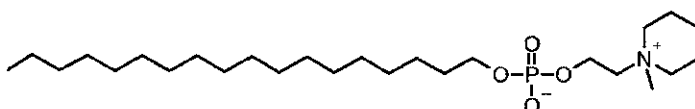
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- 21 -

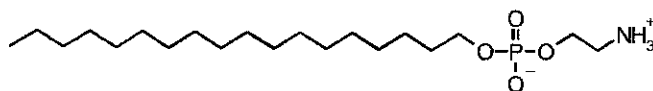
Compound 51

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Compound 52

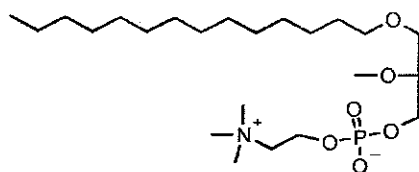
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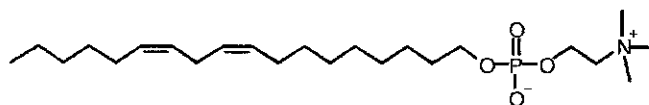
Compound 53

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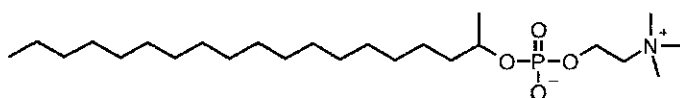
Compound 54

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Compound 55

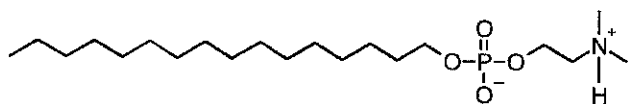
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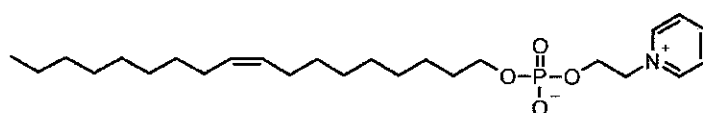
Compound 56

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- 22 -

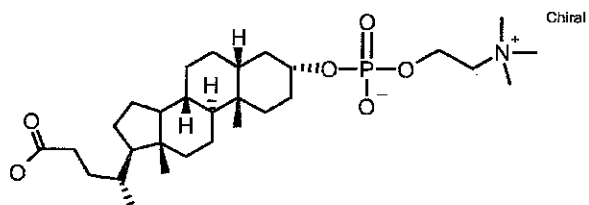
Compound 57

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Compound 58

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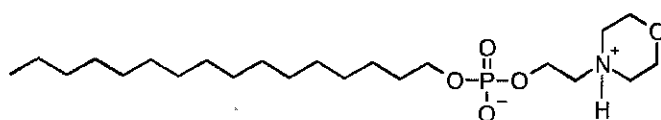
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Compound 59

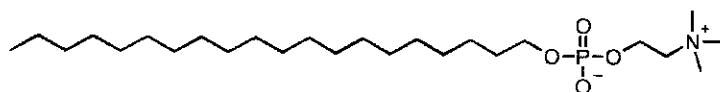
Chiral

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Compound 60

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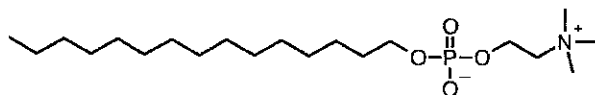
Compound 61

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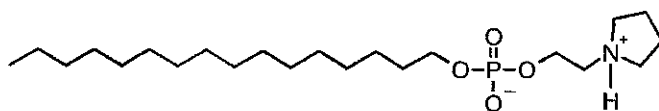
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- 23 -

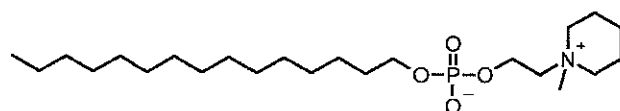
Compound 62

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Compound 63

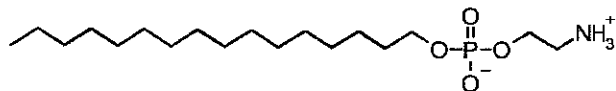
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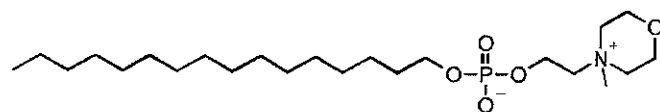
Compound 64

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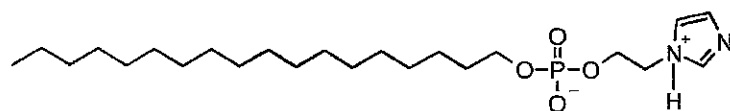
Compound 65

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Compound 66

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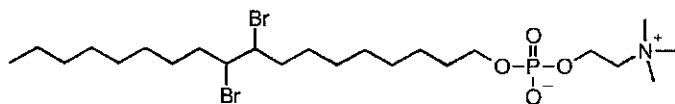
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Compound 67

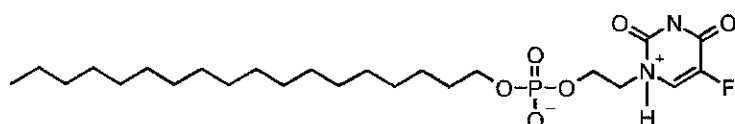
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- 24 -

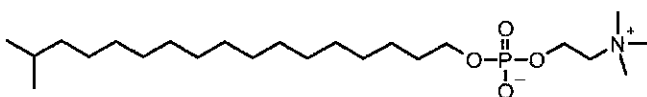
Compound 68

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Compound 69

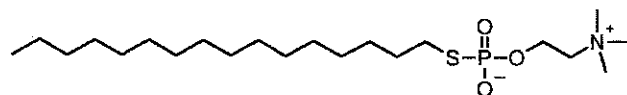
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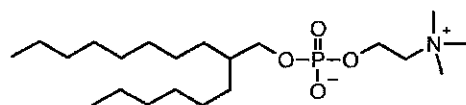
Compound 70

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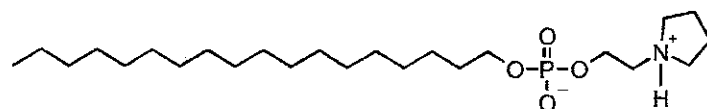
Compound 71

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Compound 72

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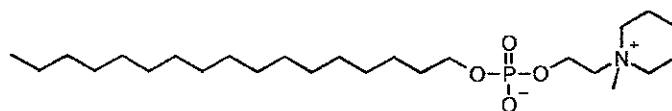
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Compound 73

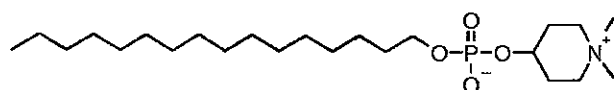
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- 25 -

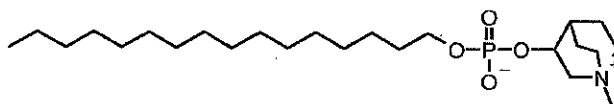
Compound 74

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Compound 75

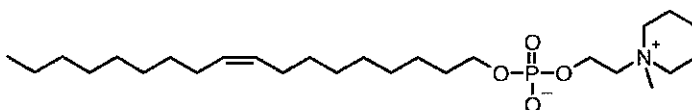
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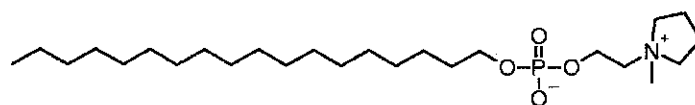
Compound 76

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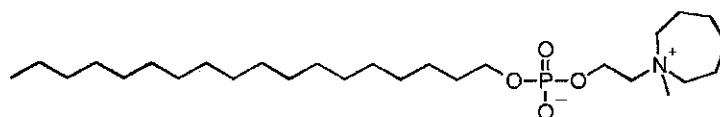
Compound 77

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Compound 78

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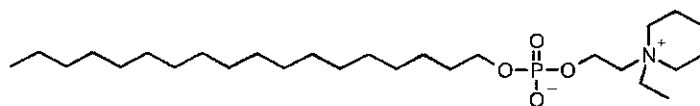
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Compound 79

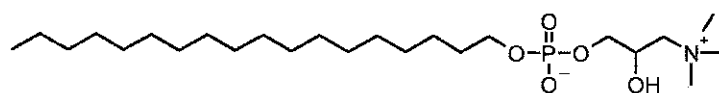
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- 26 -

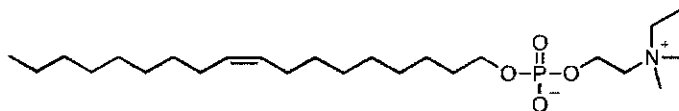
Compound 80

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Compound 81

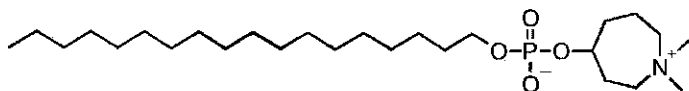
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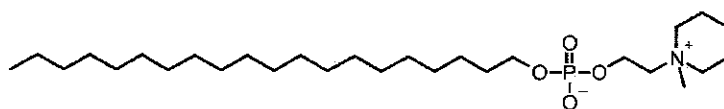
Compound 82

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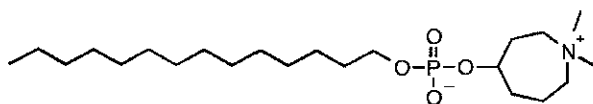
Compound 83

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Compound 84

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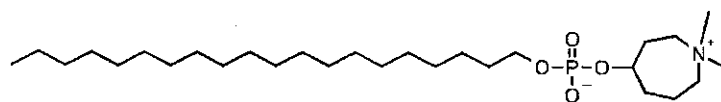
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Compound 85

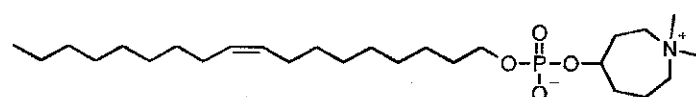
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- 27 -

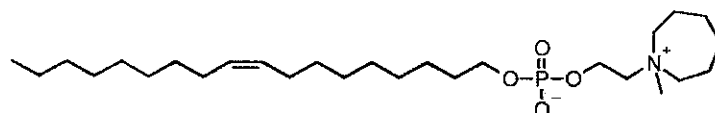
Compound 86

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Compound 87

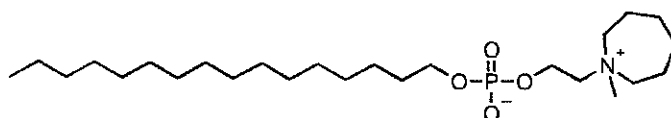
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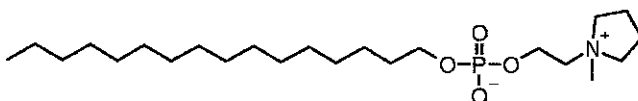
Compound 88

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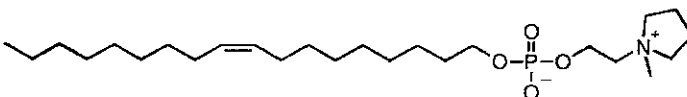
Compound 89

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Compound 90

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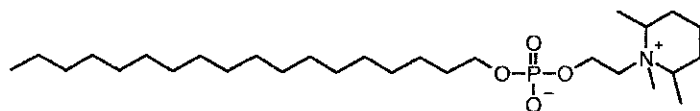
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Compound 91

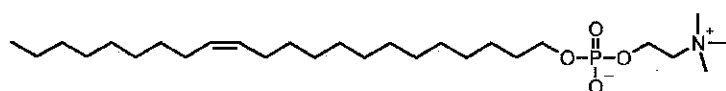
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- 28 -

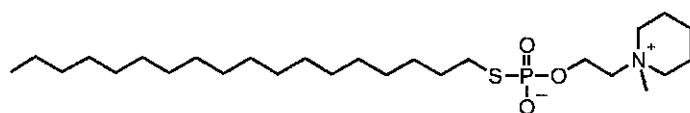
Compound 92

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Compound 93

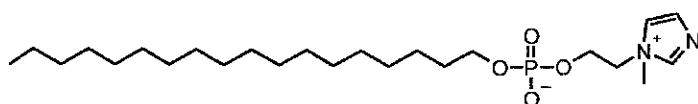
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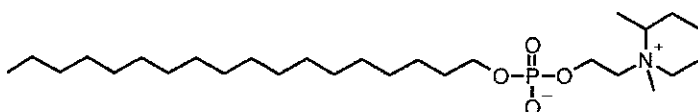
Compound 94

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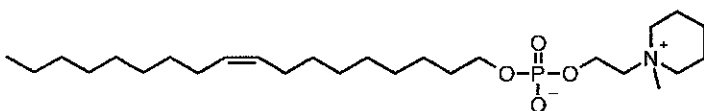
Compound 95

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Compound 96

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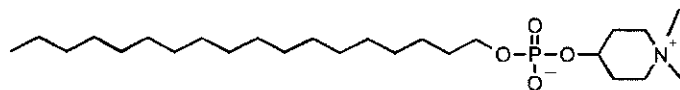
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Compound 97

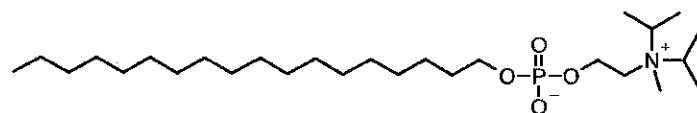
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- 29 -

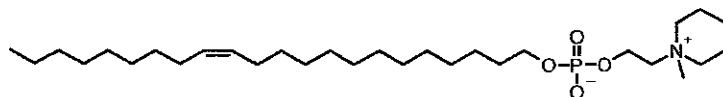
Compound 98

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Compound 99

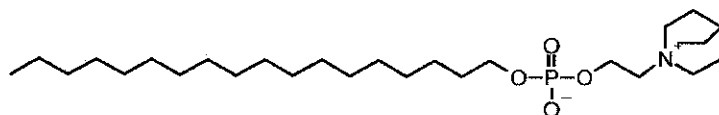
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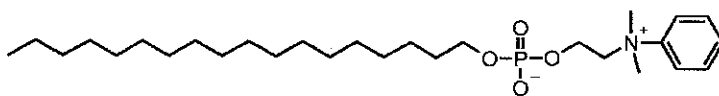
Compound 100

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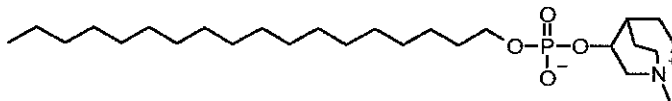
Compound 101

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Compound 102

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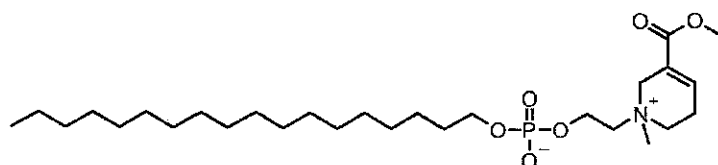
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Compound 103

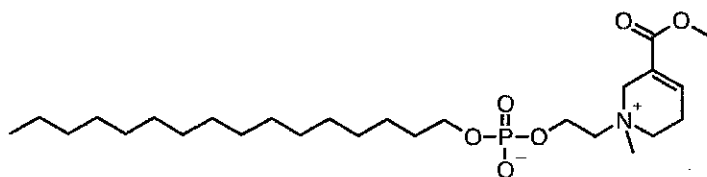
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- 30 -

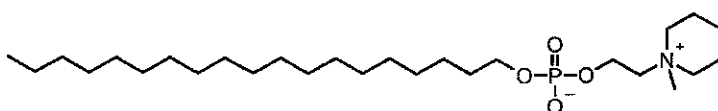
Compound 104

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Compound 105

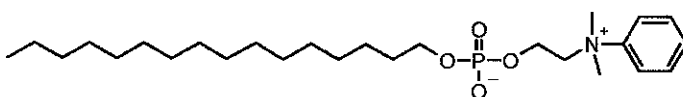
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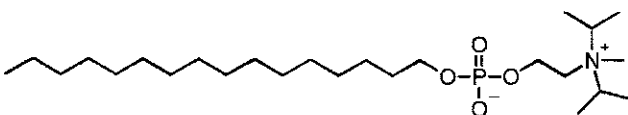
Compound 106

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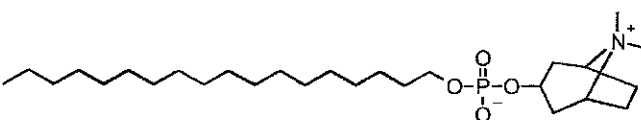
Compound 107

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Compound 108

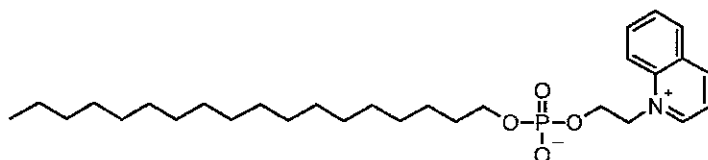
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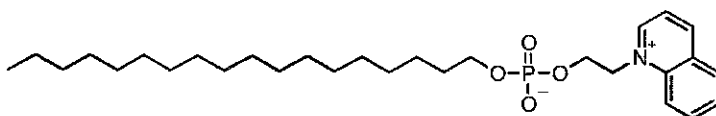
Compound 109

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- 31 -

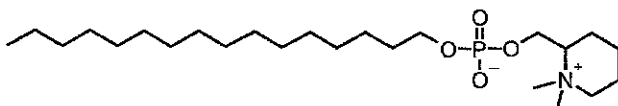
Compound 110

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Compound 111

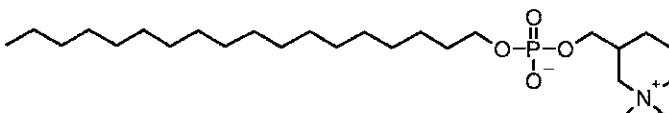
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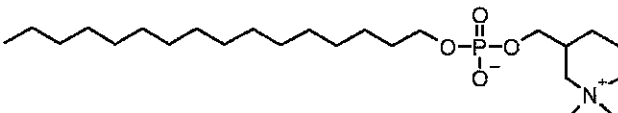
Compound 112

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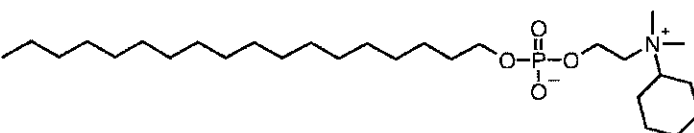
Compound 113

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Compound 114

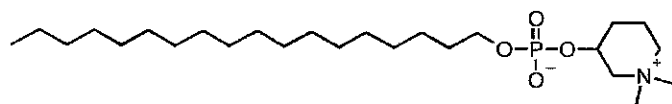
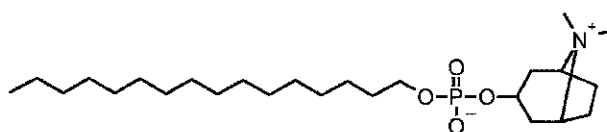
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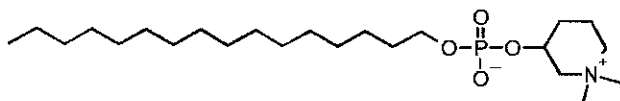
Compound 115

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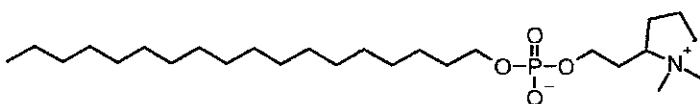
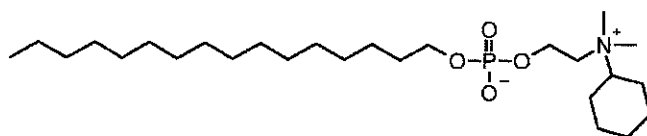
- 32 -

Compound 116**Compound 117**

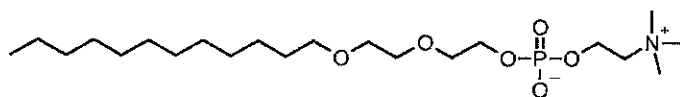
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Compound 118

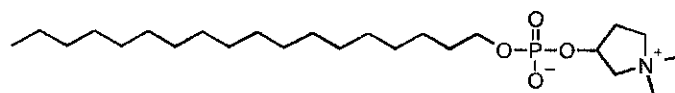
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Compound 119**Compound 120**

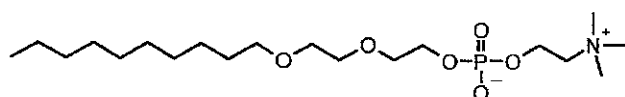
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Compound 121

- 33 -

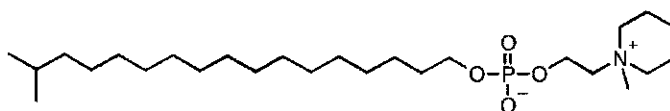
Compound 122

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Compound 123

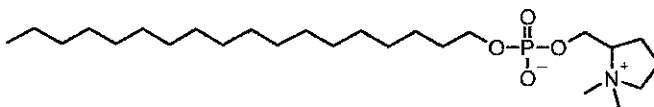
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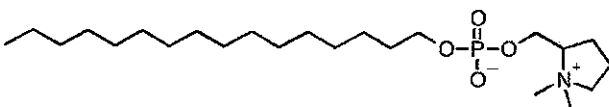
Compound 124

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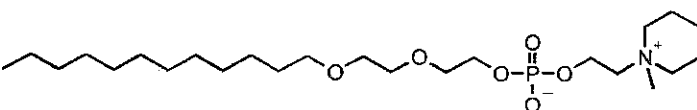
Compound 125

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Compound 126

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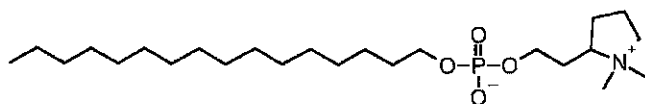
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Compound 127

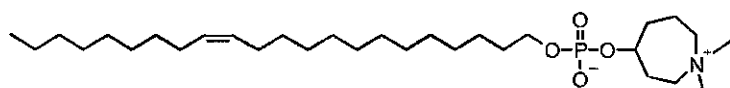
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- 34 -

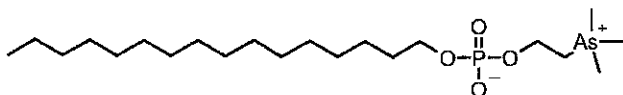
Compound 128

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Compound 129

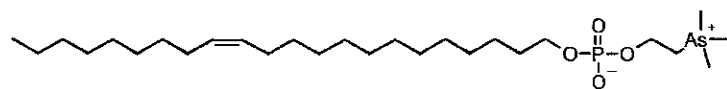
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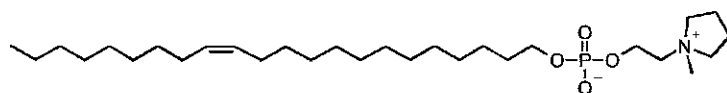
Compound 130

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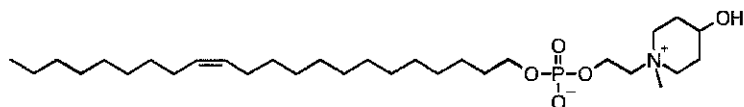
Compound 131

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Compound 132

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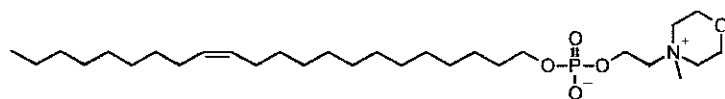
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Compound 133

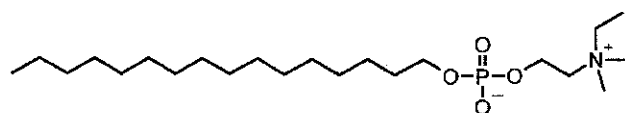
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- 35 -

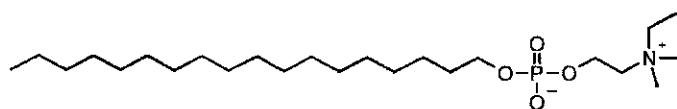
Compound 134

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Compound 135

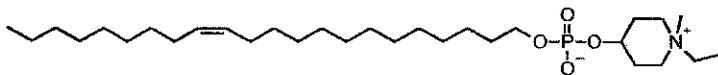
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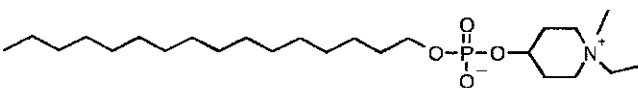
Compound 136

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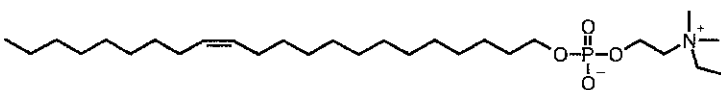
Compound 137

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Compound 138

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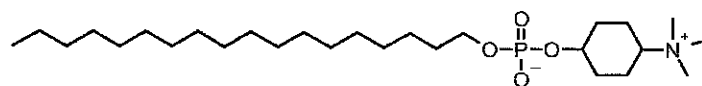
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Compound 139

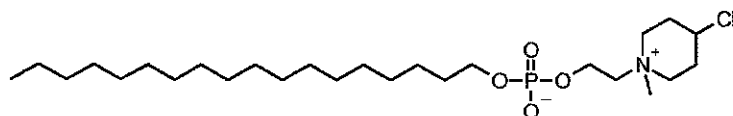
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- 36 -

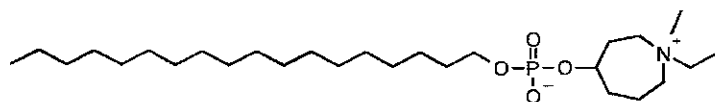
Compound 140

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Compound 141

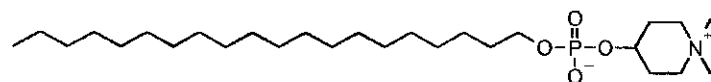
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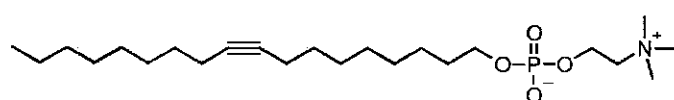
Compound 142

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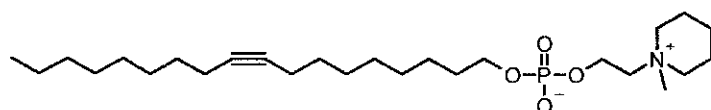
Compound 143

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Compound 144

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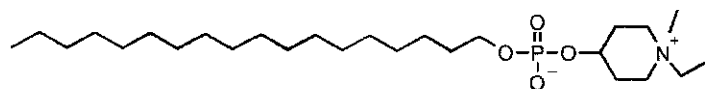
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Compound 145

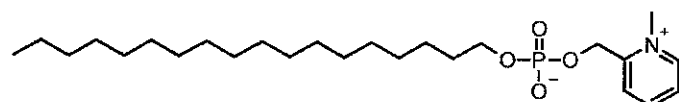
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- 37 -

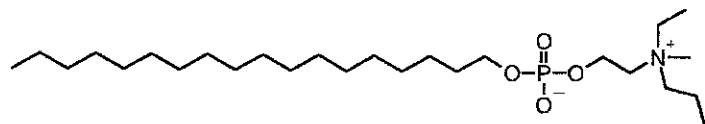
Compound 146

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Compound 147

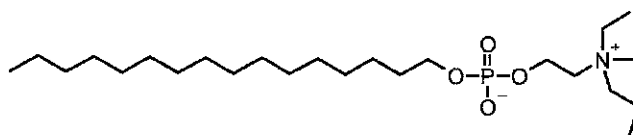
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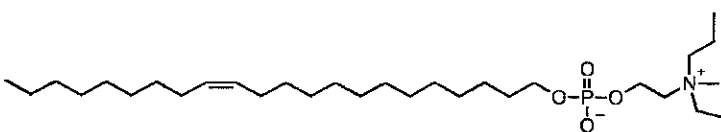
Compound 148

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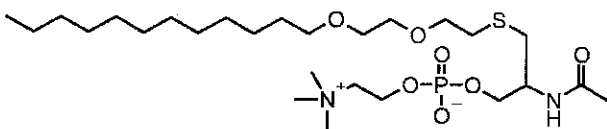
Compound 149

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Compound 150

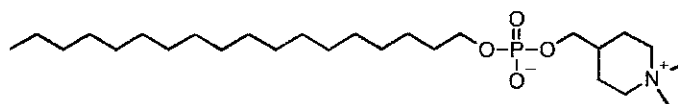
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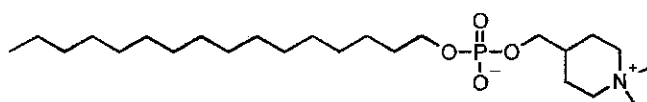
Compound 151

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- 38 -

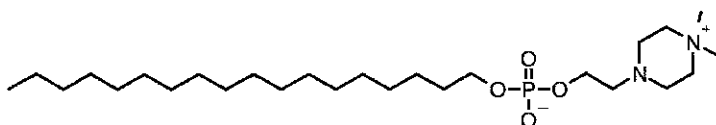
Compound 152

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Compound 153

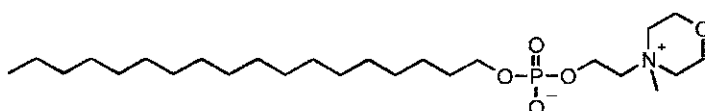
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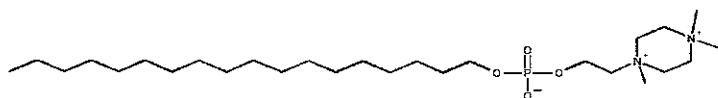
Compound 154

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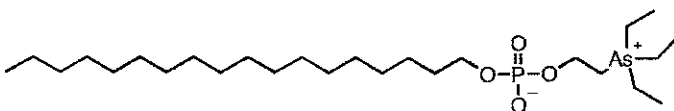
Compound 155

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Compound 156

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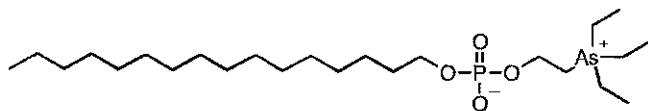
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Compound 157

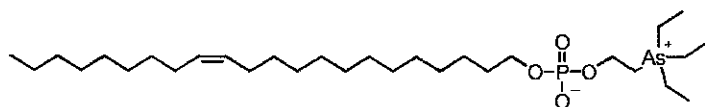
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- 39 -

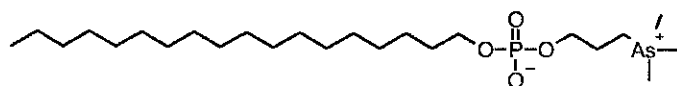
Compound 158

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Compound 159

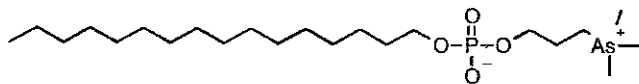
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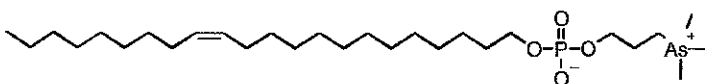
Compound 160

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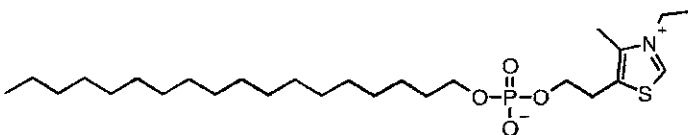
Compound 161

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Compound 162

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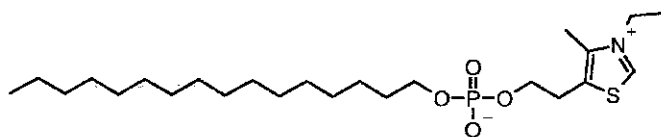
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Compound 163

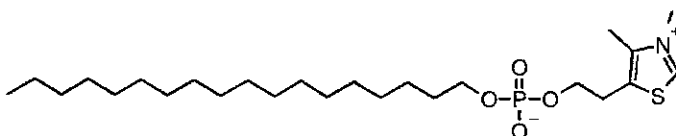
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- 40 -

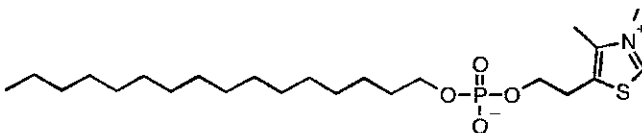
Compound 164

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Compound 165

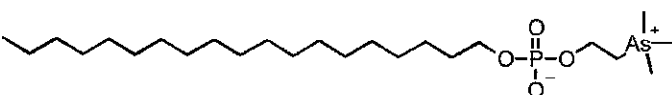
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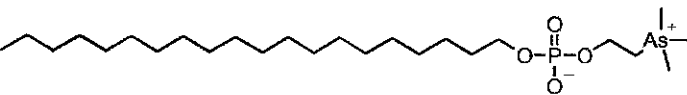
Compound 166

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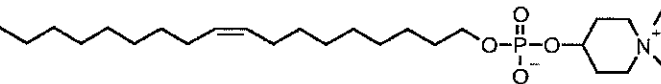
Compound 167

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Compound 168

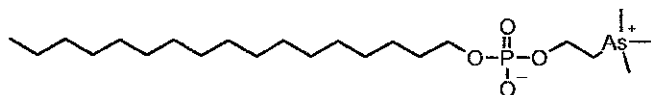
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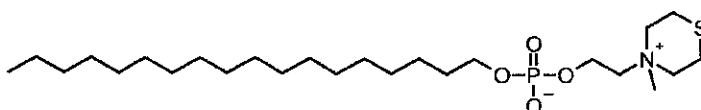
Compound 169

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- 41 -

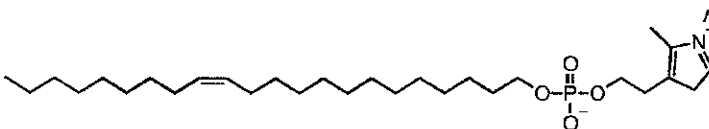
Compound 170

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Compound 171

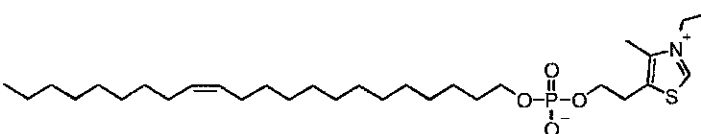
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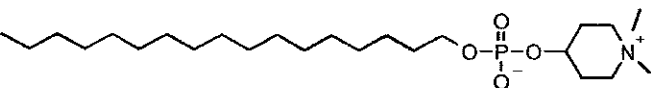
Compound 172

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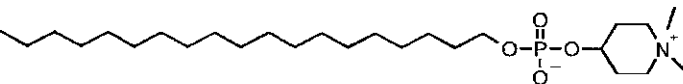
Compound 173

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Compound 174

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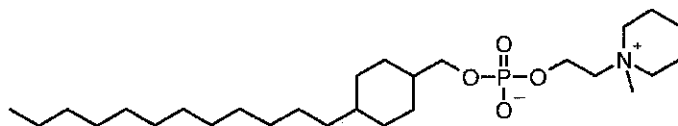
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Compound 175

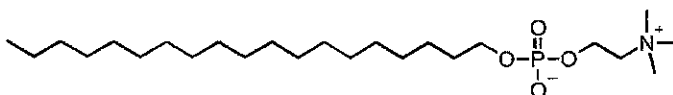
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- 42 -

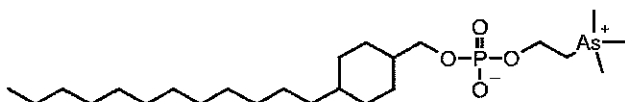
Compound 176

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Compound 177

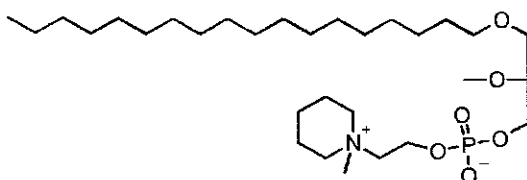
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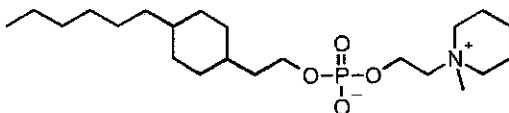
Compound 178

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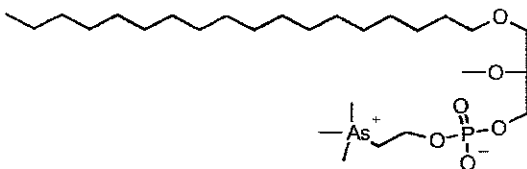
Compound 179

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Compound 180

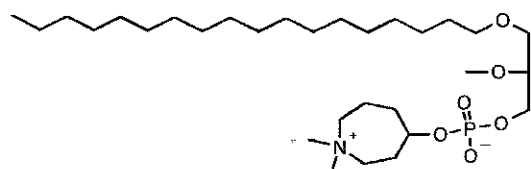
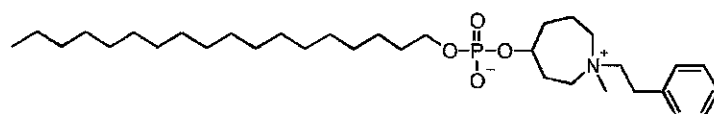
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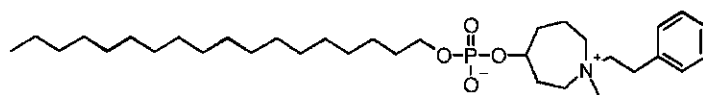
Compound 181

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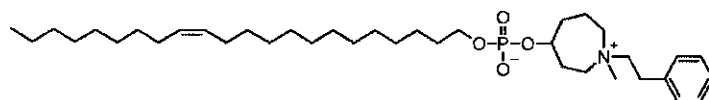
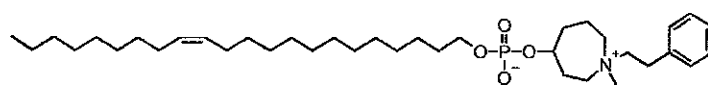
- 43 -

Compound 182**Compound 183**

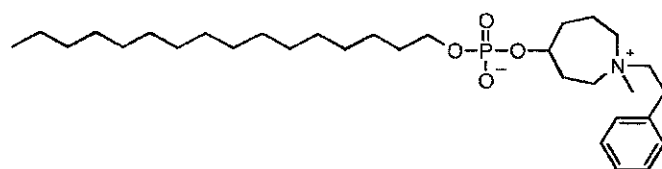
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Compound 184

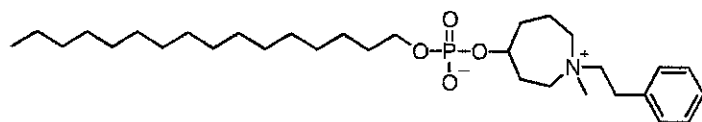
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Compound 185**Compound 186**

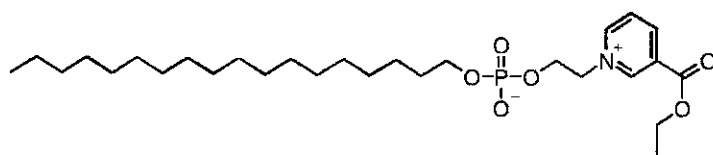
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Compound 187

- 44 -

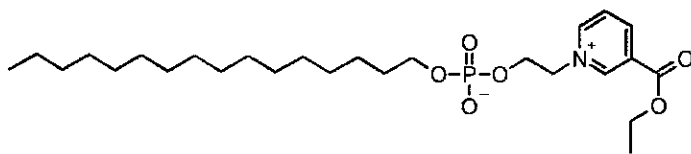
Compound 188

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Compound 189

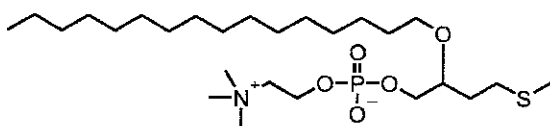
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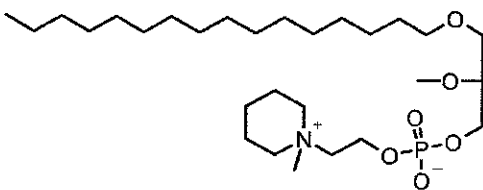
Compound 190

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Compound 191

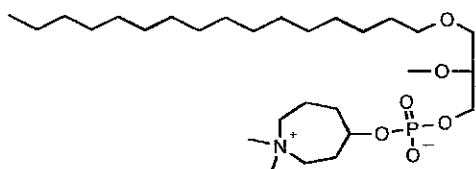
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Compound 192

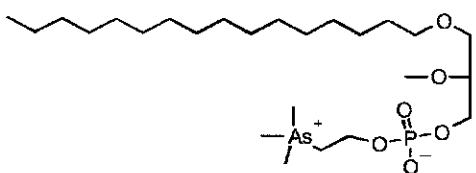
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- 45 -

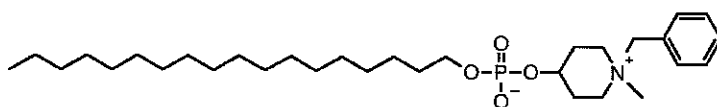
Compound 193

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Compound 194

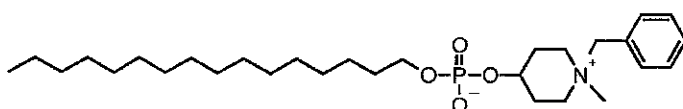
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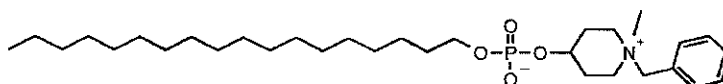
Compound 195

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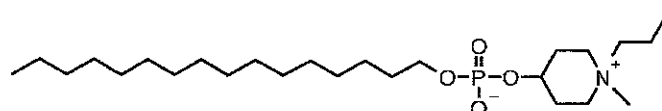
Compound 196

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Compound 197

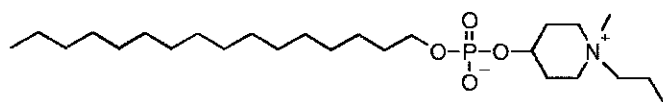
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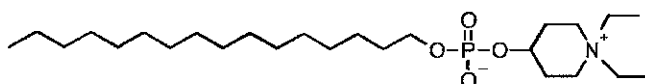
Compound 198

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- 46 -

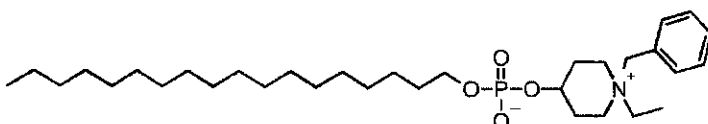
Compound 199

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Compound 200

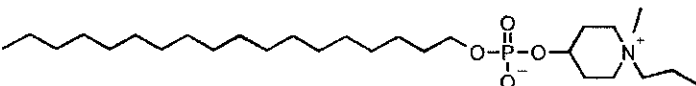
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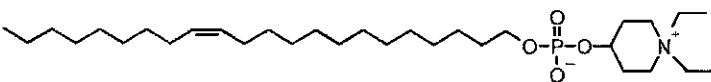
Compound 201

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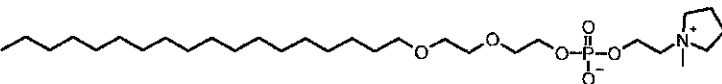
Compound 202

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Compound 203

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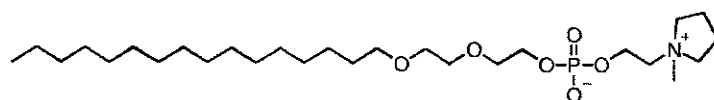
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Compound 204

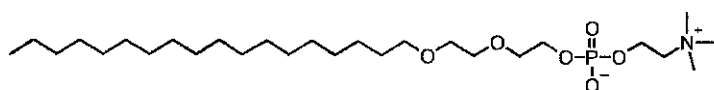
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- 47 -

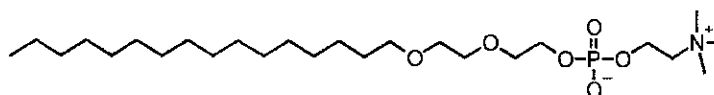
Compound 205

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Compound 206

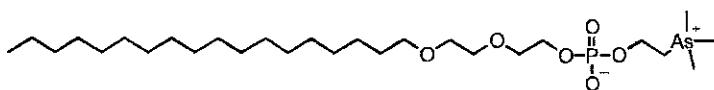
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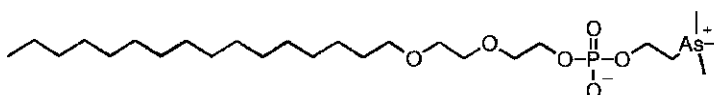
Compound 207

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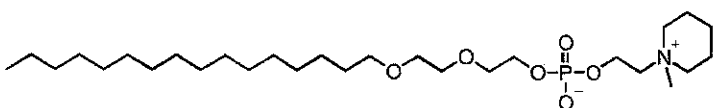
Compound 208

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Compound 209

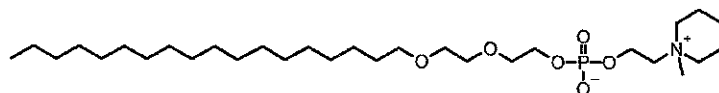
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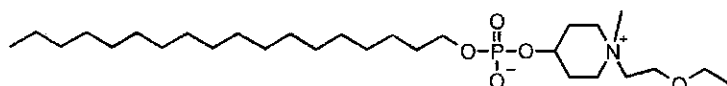
Compound 210

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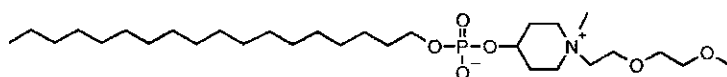
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Compound 211

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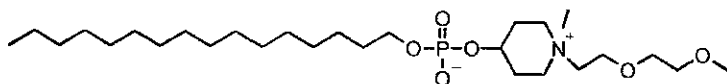
Compound 212

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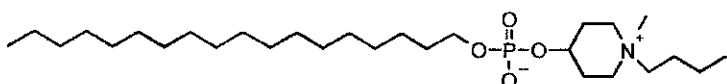
Compound 213

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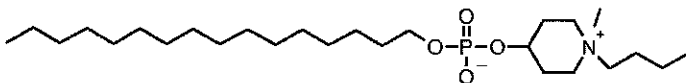
Compound 214

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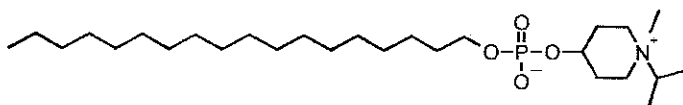
Compound 215

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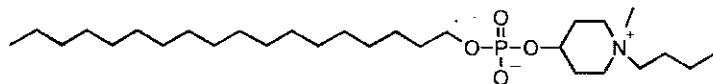
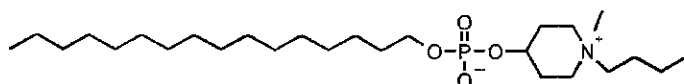
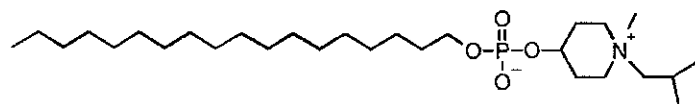
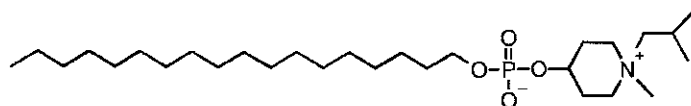
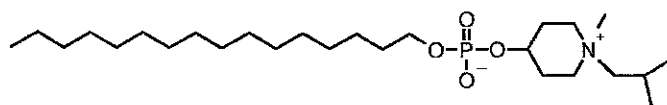
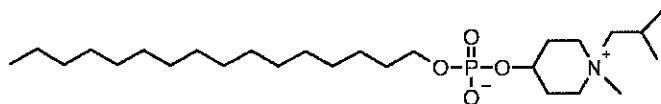
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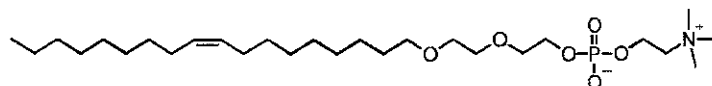
Compound 216

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Compound 217

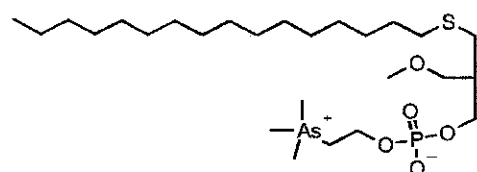
- 49 -

Compound 218**Compound 219****Compound 220****Compound 221****Compound 222****Compound 223**

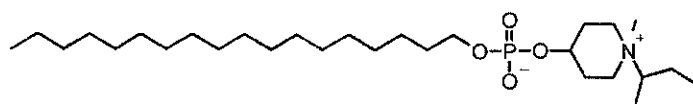
Compound 224

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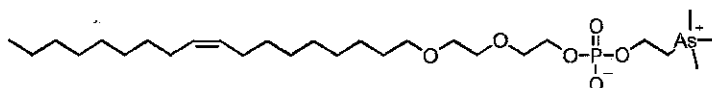
Compound 225

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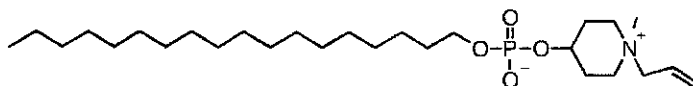
Compound 226

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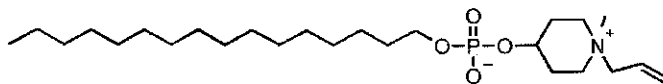
Compound 227

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Compound 228

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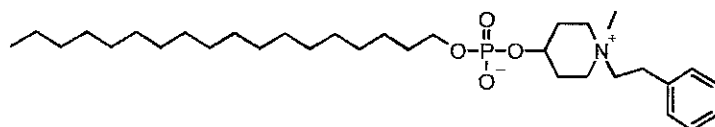
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Compound 229

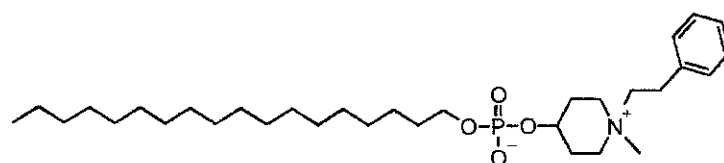
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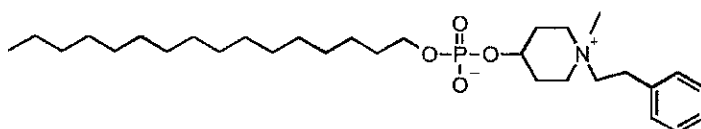
- 51 -

Compound 230

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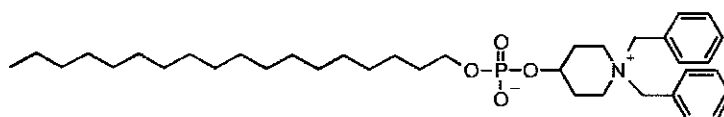
5 Compound 231

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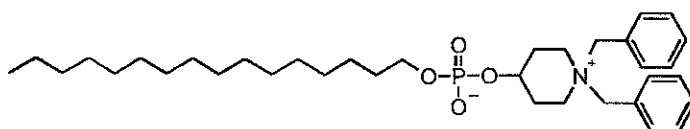
Compound 232

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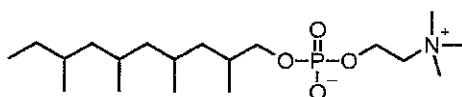
Compound 233

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Compound 234

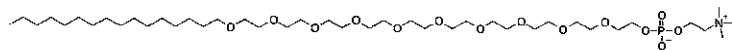
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Compound 235

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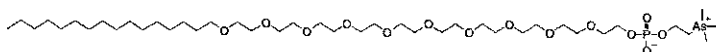
- 52 -

Compound 236

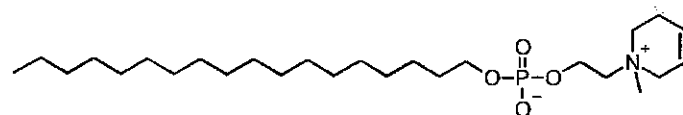
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Compound 237

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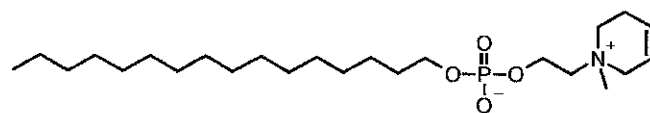


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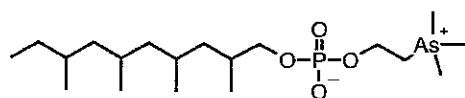
Compound 238

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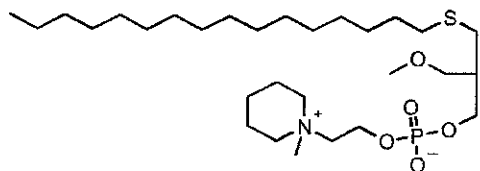
Compound 239

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Compound 240

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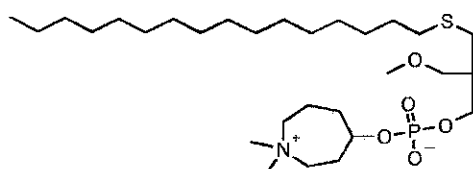
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Compound 241

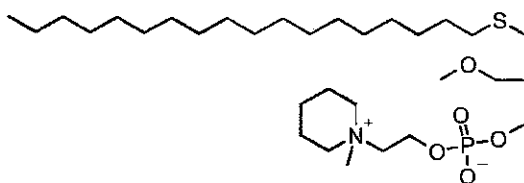
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- 53 -

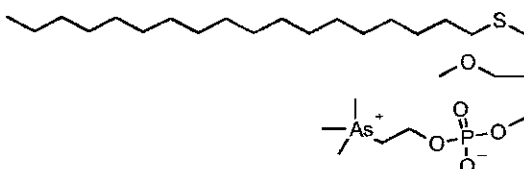
Compound 242

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Compound 243

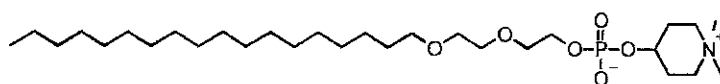
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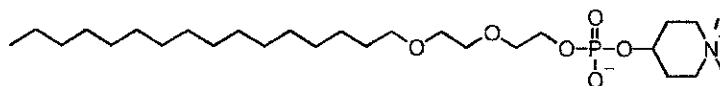
Compound 244

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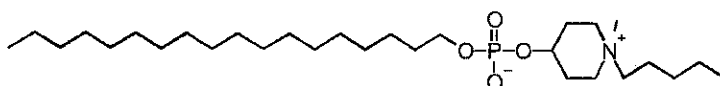
Compound 245

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Compound 246

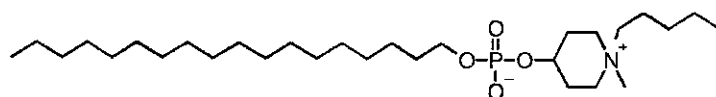
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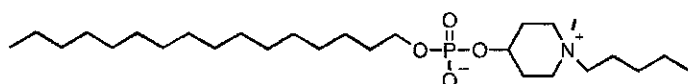
Compound 247

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- 54 -

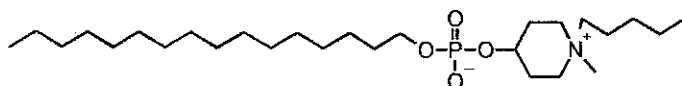
Compound 248

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Compound 249

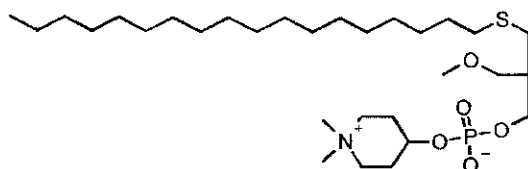
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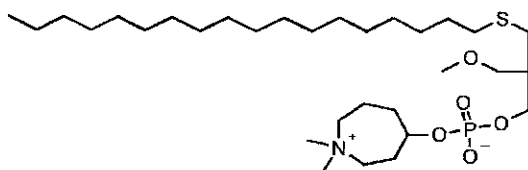
Compound 250

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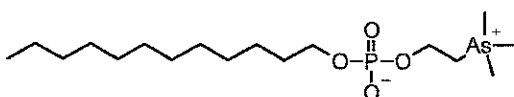
Compound 251

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Compound 252

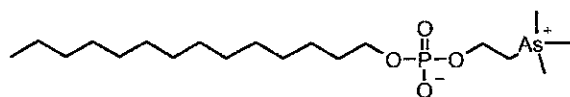
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Compound 253

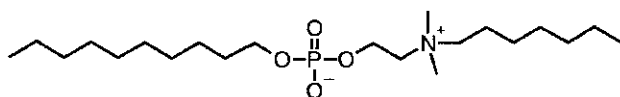
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Compound 254



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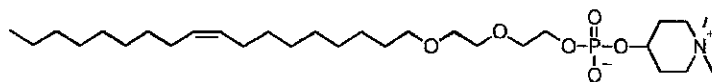
Compound 255



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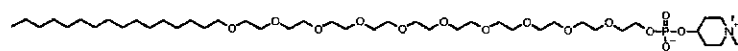
Compound 256



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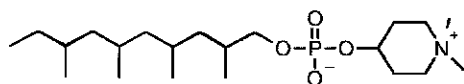
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Compound 257



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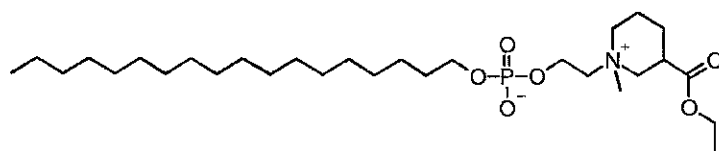
Compound 258



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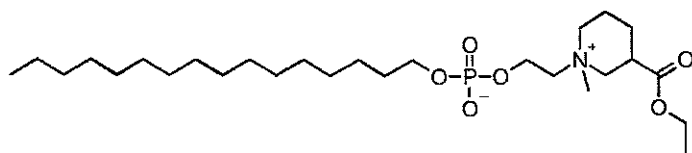
Compound 259



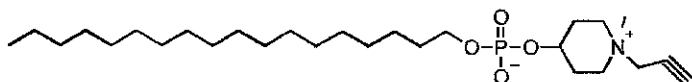
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- 56 -

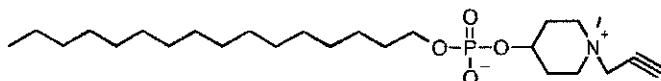
Compound 260

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Compound 261

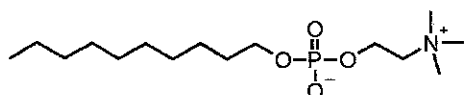
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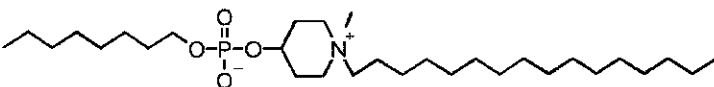
Compound 262

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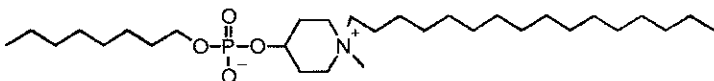
Compound 263

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Compound 264

15

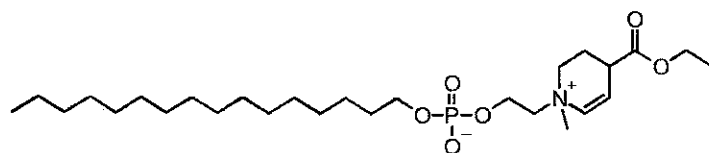
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Compound 265

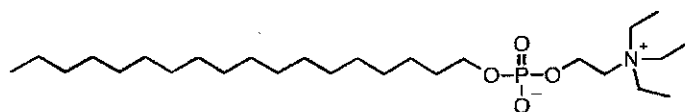
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- 57 -

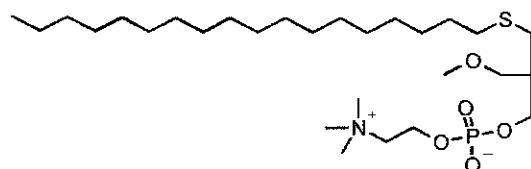
Compound 266

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Compound 267

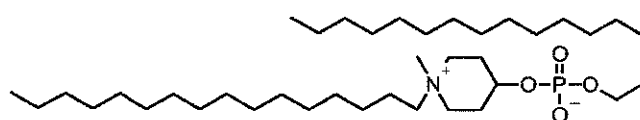
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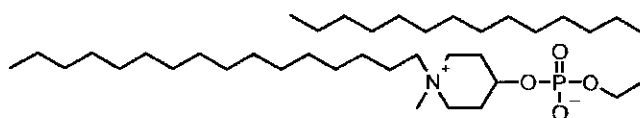
Compound 268

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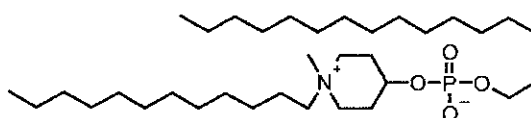
Compound 269

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Compound 270

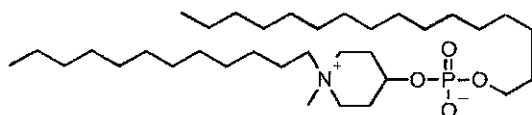
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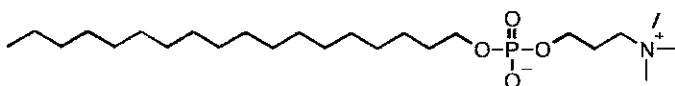
Compound 271

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- 58 -

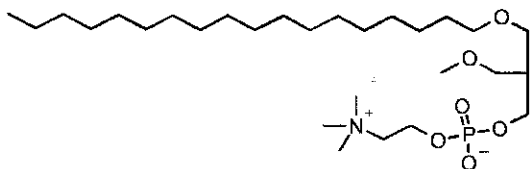
Compound 272

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Compound 273

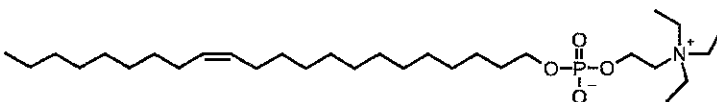
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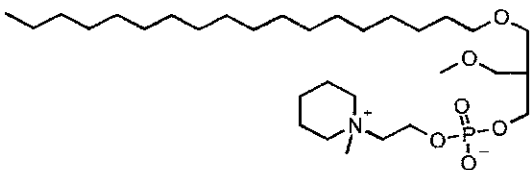
Compound 274

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Compound 275

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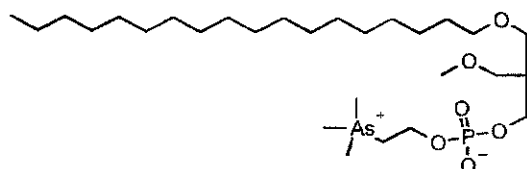
Compound 276

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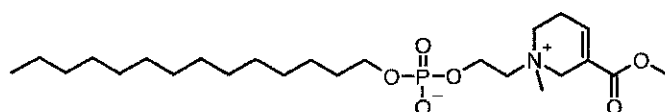
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- 59 -

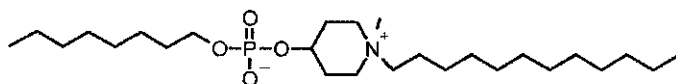
Compound 277

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Compound 278

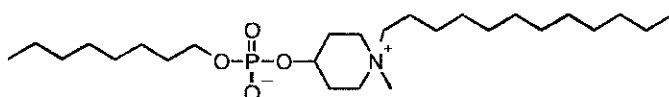
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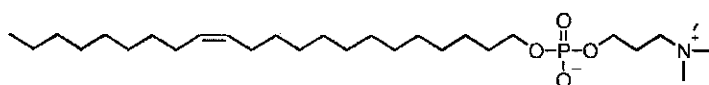
Compound 279

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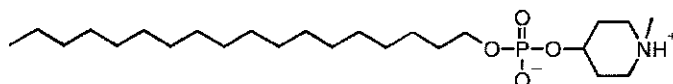
Compound 280

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Compound 281

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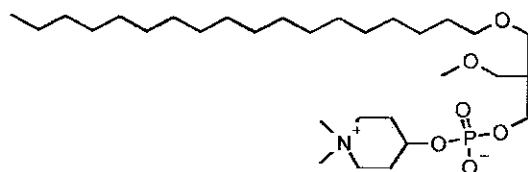
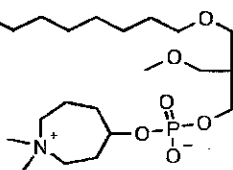
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Compound 282

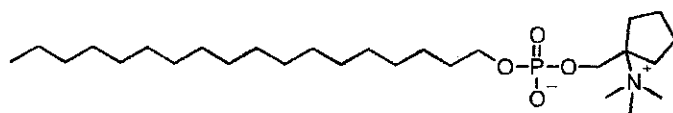
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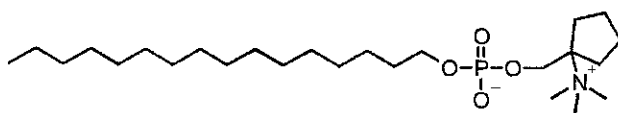
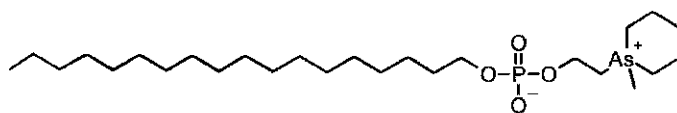
- 60 -

Compound 283**Compound 284**

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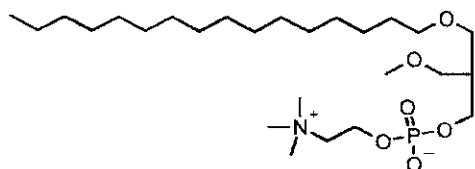
Compound 285

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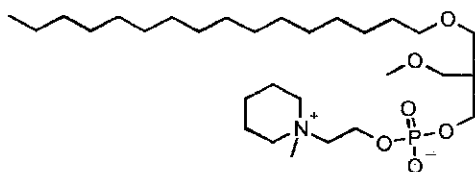
Compound 286**Compound 287**

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- 61 -

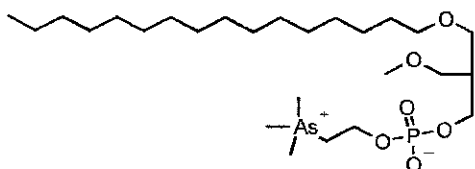
Compound 288

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Compound 289

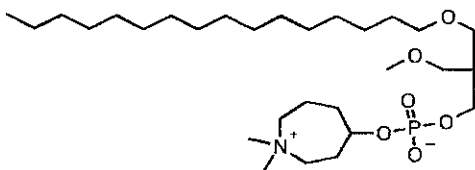
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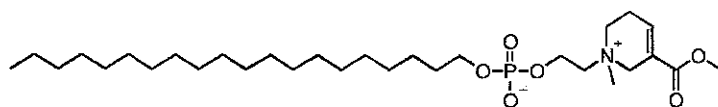
Compound 290

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Compound 291

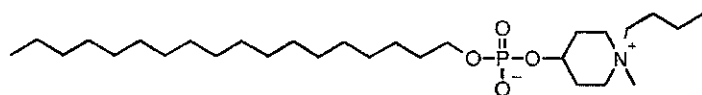
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Compound 292

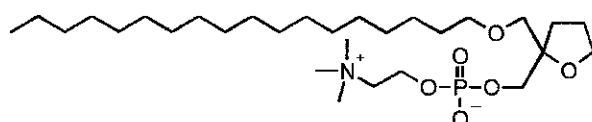
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- 62 -

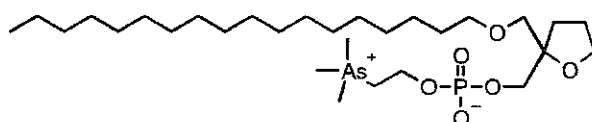
Compound 293

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Compound 294

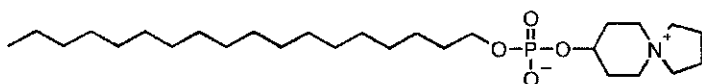
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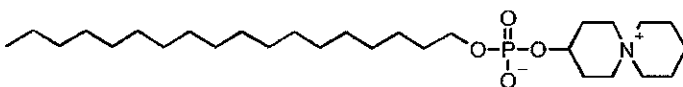
Compound 295

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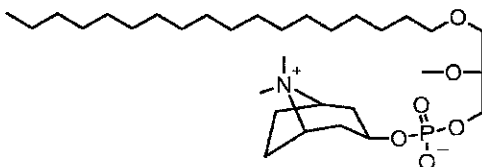
Compound 296

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Compound 297

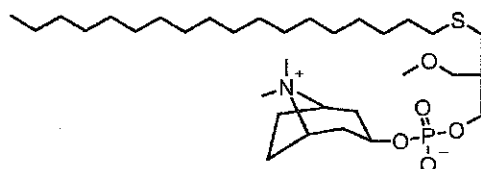
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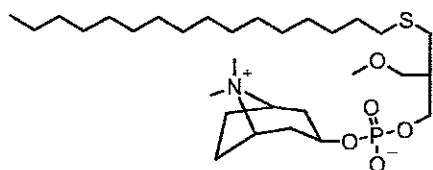
Compound 298

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- 63 -

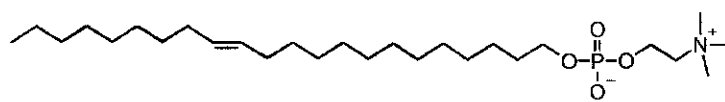
Compound 299

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Compound 300

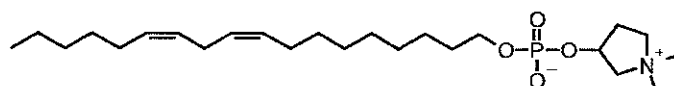
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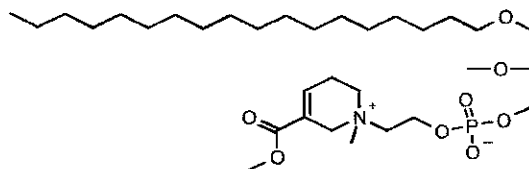
Compound 301

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Compound 302

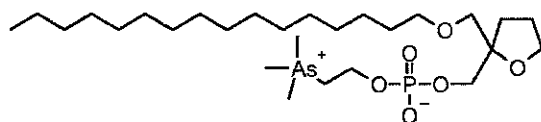
;

Compound 303

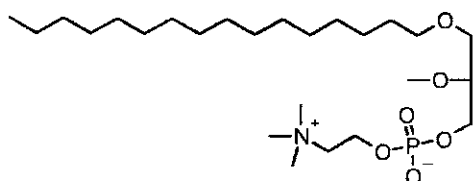
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- 64 -

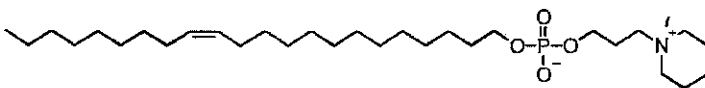
Compound 304

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Compound 305

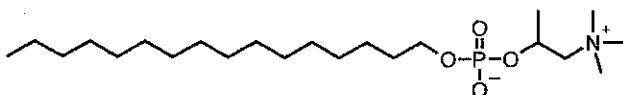
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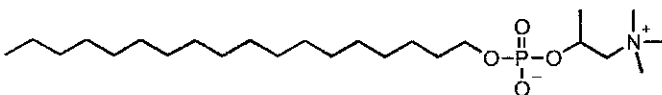
Compound 306

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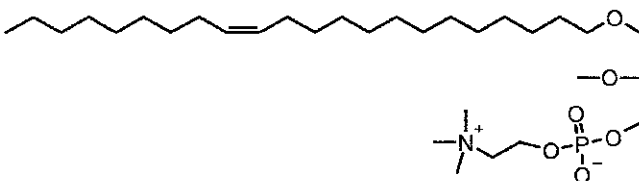
Compound 307

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Compound 308

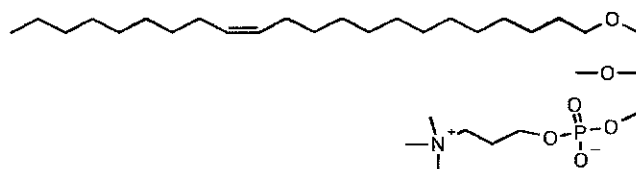
15

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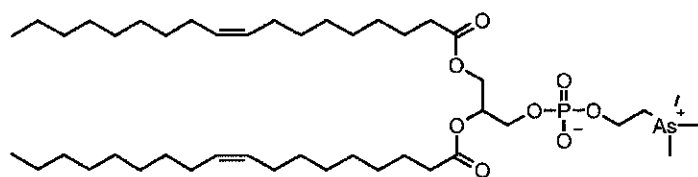
Compound 309

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- 65 -

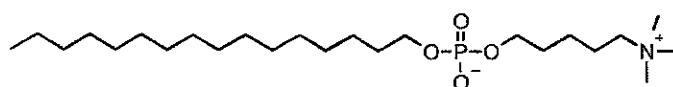
Compound 310

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Compound 311

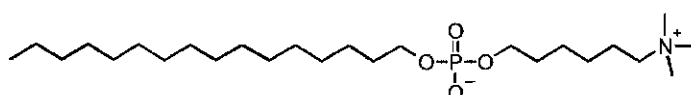
5

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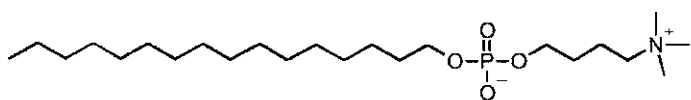
Compound 312

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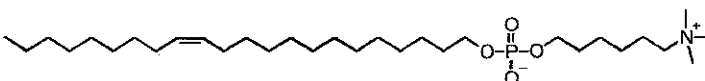
Compound 313

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Compound 314

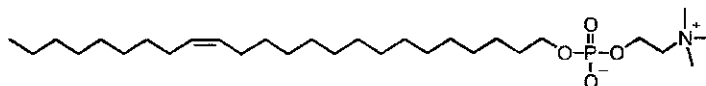
15

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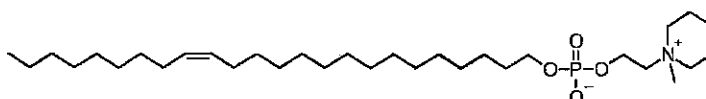
Compound 315

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- 66 -

Compound 316

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Compound 317

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“

These alkyl phospholipid derivatives (Compounds 1 to 317) can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

10

For the avoidance of doubt, if chemical name and chemical structure of the above illustrated compounds do not correspond by mistake, the chemical structure is regarded to unambiguously define the compound.

15 In a preferred embodiment, all the above generically or explicitly disclosed alkyl phospholipid derivatives, including preferred subsets of formula (I) and Compounds 1 to 317, hereinafter referred to as compounds of the (present) invention, can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where
 20 the microorganism is selected from the group consisting of “bacterium, fungus, protozoon and/or virus”.

The terms indicated for explanation of the above compounds of the invention always, unless indicated otherwise in the description or in the claims, have the
 25 following meanings:

The term “unsubstituted” means that the corresponding radical, group or moiety has no substituents.

The term "substituted" means that the corresponding radical, group or moiety has one or more substituents. Where a radical has a plurality of substituents, and a selection of various substituents is specified, the substituents are selected independently of one another and do not need to be identical.

5

The term "alkyl" includes for the purposes of this invention acyclic and cyclic saturated, unsaturated or partially unsaturated hydrocarbons which may be straight-chain or branched or cyclic or also include cyclic hydrocarbons as part of a straight-chained or branched hydrocarbon system and which may contain one or more double
10 and/or triple bonds. In this connection, C1-C6alkyl, C1-C12alkyl, C1-C18alkyl, C8-C30alkyl and the like refer to above definition having 1 to 6, 1 to 12, 1 to 18, 8 to 30, respectively, and the like carbon atoms.

Examples of suitable alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, tert-pentyl, 2- or 3-methyl-
15 pentyl, n-hexyl, 2-hexyl, isohexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tetradecyl, n-hexadecyl, n-octadecyl, n-icosanyl, n-docosanyl, ethylenyl (vinyl), propenyl ($-\text{CH}_2\text{CH}=\text{CH}_2$; $-\text{CH}=\text{CH}-\text{CH}_3$, $-\text{C}(=\text{CH}_2)-\text{CH}_3$), butenyl, pentenyl, hexenyl, heptenyl, octenyl, octadienyl, octadecenyl, octadec-9-enyl, icosenyl, icos-11-enyl, (Z)-icos-11-enyl, docosyl, docos-13-enyl, (Z)-docos-13-enyl, ethynyl, propynyl ($-\text{CH}_2-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{C}-\text{CH}_3$),
20 butynyl, pentynyl, hexynyl, heptynyl, octynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclohexenyl, cyclopentenyl, cyclooctadienyl.

The term "C3-C8cycloalkyl" stands for a saturated or partially unsaturated non-
25 aromatic cyclic hydrocarbon group/radical, containing 3 to 8 carbon atoms that may optionally be linked via an alkyl group where the alkyl has the meaning as defined herein, preferably a (C3-C8)-cycloalkyl-(C1-C4)-alkyl radical. Such "C3-C8cycloalkyl" radicals can be linked via any ring member.

Examples of suitable cycloalkyl radicals are cyclopropyl, cyclobutyl, cyclopentyl,
30 cyclohexyl, cycloheptyl, cyclooctyl, cyclohexenyl, cyclopentenyl, cyclooctadienyl, cyclopropylmethyl, cyclohexylmethyl, cyclopentylethyl, cyclohexenylethyl.

The term "steroid moiety" for the purpose of the present invention refers to a basic

steroid structure as for instance illustrated on page 131 in "Organische Chemie" by K. Peter C. Vollhardt (VCH Weinheim, 1. korrigierter Nachdruck, 1990, der 1. Auflage 1988, ISBN 3-527-26912-6). Such "steroid moiety" can be linked via any atom of the moiety.

5

The term "aryl" refers to aromatic hydrocarbon systems having 3 to 14, preferably 5 to 14, carbon atoms. The term "aryl" also includes systems in which the aromatic cycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system, such as where the aromatic cycle is fused to an "aryl", "C3-C8cycloalkyl", "heteroaryl" or "heterocyclyl" group as defined herein via any desired and possible ring member of the aryl radical. Such "aryl" radicals can be linked via any ring member. Examples of "aryl" are inter alia phenyl, biphenyl, naphthyl and anthracenyl, but also indanyl, indenyl, or 1,2,3,4-tetrahydronaphthyl. The term "aryl" is also intended to comprise radicals in which the aryl radical is linked via a C1-C18alkyl group, preferably C1-C12alkyl group. Most preferred are aryl-C1-C4alkyl radicals, preferably benzyl or phenylethyl radicals.

The term "heteroaryl" refers to a 5-, 6- or 7-membered cyclic aromatic radical which comprises at least 1, where appropriate also 2, 3, 4 or 5 heteroatoms, preferably nitrogen, oxygen and/or sulfur, where the heteroatoms are identical or different. The number of nitrogen atoms is preferably 0, 1, 2, or 3, and that of the oxygen and sulfur atoms is independently 0 or 1. The term "heteroaryl" also includes systems in which the aromatic cycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system, such as where the aromatic cycle is fused to an "aryl", "C3-C8cycloalkyl", "heteroaryl" or "heterocyclyl" group as defined herein via any desired and possible ring member of the heteroaryl radical. Such "heteroaryl" radicals can be linked via any ring member. Examples of "heteroaryl" include pyrrolyl, thienyl, furyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, isoxazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazolyl, tetrazolyl, pyridazinyl, phthalazinyl, indazolyl, indolizynyl, quinoxalynyl, quinazolinyl, pteridinyl, carbazolyl, phenazinyl, phenoxazinyl, phenothiazinyl, acridinyl. The terms "heteroaryl" is also intended to comprise radicals in which the heteroaryl radical is linked via a C1-C18alkyl group, preferably C1-C12alkyl group. Most preferred are heteroaryl-C1-C4alkyl radicals, preferably indolyl-(C₁-C₄)-alkyl radicals, such as 1*H*-indole-3-yl-methyl or 2-(1*H*-indole-3-yl)-ethyl.

The term "heterocyclyl" refers to a mono- or polycyclic system of 3 to 20, preferably 5 or 6 to 14 ring atoms comprising carbon atoms and 1, 2, 3, 4, or 5 heteroatoms, in particular nitrogen, oxygen and/or sulfur which are identical or different. The cyclic system may be saturated, mono- or polyunsaturated but may not be aromatic. In the case of a cyclic system consisting of at least two rings the rings may be fused or spiro- or otherwise connected. Such "heterocyclyl" radicals can be linked via any ring member. The term "heterocyclyl" also includes systems in which the heterocycle is part of a bi- or polycyclic saturated, partially unsaturated and/or aromatic system, such as where the heterocycle is fused to an "aryl", "C3-C8cycloalkyl", "heteroaryl" or "heterocyclyl" group as defined herein via any desired and possible ring member of the heterocyclyl radical. Examples of "heterocyclyl" include pyrrolidinyl, thiapyrrolidinyl, piperidinyl, piperazinyl, oxapiperazinyl, oxapiperidinyl, oxadiazolyl, tetrahydrofuryl, imidazolidinyl, thiazolidinyl, tetrahydropyranyl, morpholinyl, tetrahydrothiophenyl, dihydropyranyl. The term "heterocyclyl" is also intended to comprise radicals in which the heterocyclyl group is linked via an C1-C18alkyl group, preferably C1-C12alkyl group. Most preferred are heterocyclyl-C1-C4alkyl radicals.

The term „alkoxy“ refers to radicals in which a „alkyl“, „C3-C8cycloalkyl“, „aryl“, „heteroaryl“, and/or „heterocyclyl“ group is linked via an oxygen atom (–O–group), where „alkyl“, „C3-C8cycloalkyl“, „aryl“, „heteroaryl“ and „heterocyclyl“ have the meanings as defined herein.

The term "halogen", "halogen atom" or "halogen substituent" (Hal-) refers to one, where appropriate, a plurality of fluorine (F, fluoro), bromine (Br, bromo), chlorine (Cl, chloro), or iodine (I, iodo) atoms. The designations "dihalogen", "trihalogen" and "perhalogen" refer respectively to two, three and four substituents, where each substituent can be selected independently from the group consisting of fluorine, chlorine, bromine and iodine. "Halogen" preferably means a fluorine, chlorine or bromine atom.

30

The term „substituted“ in connection with „steroid moiety“, „alkyl“, in particular C1-C6alkyl, C1-C12alkyl, C1-C18alkyl, C8-C30alkyl, „C3-C8cycloalkyl“, „aryl“, „heteroaryl“, „heterocyclyl“, "heterocycle" and „alkoxy“, unless not explicitly otherwise defined in the

description or in the claims, means the independent replacement/substitution of one or more hydrogen atoms by a substituent independently selected from the group consisting of “-NO₂, -NO, -CN, -OH, halogen, F, Cl, Br, I, -NH₂, -NHNH₂, -N₃, -SH, -SO₃H, -COOH, -CONH₂, -CHO, -CHNOH, -NH-C(NH₂)=NH, -C(NH₂)=NH, -CF₃, -OCF₃, -OSO₃H, -OP(O)(OH)₂, -P(O)(OH)₂, -NH-(C1-C12alkyl), -N(C1-C12alkyl)₂, -NH-aryl, -N(aryl)₂, -N-A5A6, -NH-C(NH₂)=N-(C1-C12alkyl), -C(NH₂)=N-(C1-C12alkyl), -NH-C(NH₂)=N-aryl, -C(NH₂)=N-aryl, -OP(O)(O-(C1-C12alkyl))₂, -OP(O)(O-aryl)₂, -OP(O)(O-heteroaryl)₂, -OP(O)(O-A7)(O-A8), -O-aryl, -O-heteroaryl, -O-(C3-C8cycloalkyl), -O-heterocyclyl, -S-(C1-C12alkyl), -S-aryl, -S-heteroaryl, -S-(C3-C8cycloalkyl), -S-heterocyclyl, -SO-(C1-C12alkyl), -SO-aryl, -SO-heteroaryl, -SO-(C3-C8cycloalkyl), -SO-heterocyclyl, -SO₂-(C1-C12alkyl), -SO₂-aryl, -SO₂-heteroaryl, -SO₂-(C3-C8cycloalkyl), -SO₂-heterocyclyl, -SO₃-(C1-C12alkyl), -SO₃-aryl, -SO₃-heteroaryl, -SO₃-(C3-C8cycloalkyl), -SO₃-heterocyclyl, -OC(O)-(C1-C12alkyl), -OC(O)-(C3-C8cycloalkyl), -OC(O)-aryl, -OC(O)-heterocyclyl, -OC(O)-heteroaryl, -C(O)-(C1-C12alkyl), -C(O)-(C3-C8cycloalkyl), -C(O)-aryl, -C(O)-heterocyclyl, -C(O)-heteroaryl, -C(O)O-(C1-C12alkyl), -C(O)O-(C3-C8cycloalkyl), -C(O)O-aryl, -C(O)O-heterocyclyl, -C(O)O-heteroaryl, -OC(O)NH-(C1-C12alkyl), -OC(O)NH-(C3-C8cycloalkyl), -OC(O)NH-aryl, -OC(O)NH-heteroaryl, -OC(O)NH-heterocyclyl, -OC(O)N-A1A2, -OC(O)N-heterocyclyl, -C(O)NH-(C1-C12alkyl), -C(O)NH-(C3-C8cycloalkyl), -C(O)NH-aryl, -C(O)NH-heteroaryl, -C(O)NH-heterocyclyl, -C(O)N-A3A4, -C(O)N-heterocyclyl, C1-C12alkyl, C3-C8cycloalkyl, aryl, heteroaryl, heterocyclyl” where A1, A2, A3, A4, A5, A6, A7, A8, A9, A10 independently are selected from the group consisting of “C1-C12alkyl, C3-C8cycloalkyl, aryl, heteroaryl, heterocyclyl”.

25

For the purpose of the present invention, the terms indicated for explanation of the above group of microorganisms always, unless indicated otherwise in the description or in the claims, have the following meanings:

The term “bacterium” or “bacteria” is intended to comprise all known aerobic bacteria, obligatory/fastidious anaerobic bacteria and facultative anaerobic bacteria. These can be either gram-positive or gram-negative or difficult to Gram stain (atypical), do also comprise spore forming bacteria and bacterial spores and can for instance be members of Actinobacteria, Aquificae, Bacteroidetes/Chlorobi, Chlamydiae/Verrucomicrobia, Chloroflexi, Chrysiogenetes, Cyanobacteria,

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Deferribacteres, Deinococcus-Thermus, Dictyoglomi, Fibrobacteres/Acidobacteria, Firmicutes, Fusobacteria, Gemmatimonadetes, Nitrospirae, Omnibacteria, Planctomycetes, Proteobacteria, Spirochaetes, Thermodesulfobacteria, Thermomicrobia and/or Thermotogae.

- 5 Examples of such bacteria are *Acinetobacter* spp., *Actinobacillus* spp., *Actinomyces* spp., *Aeromonas* spp., *Agrobacterium* spp., *Alcaligenes* spp., *Anaplasma* spp., *Aquifex* spp., *Bacillus* spp., *Bacteroides* spp., *Bifidobacterium* spp., *Bordetella* spp., *Borrelia* spp., *Bradyrhizobium* spp., *Branhamella* spp., *Brucella* spp., *Buchnera* spp., *Burkholderia* spp., *Campylobacter* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Caulobacter* spp., *Chlamydia* spp., *Chlamydophila* spp., *Chlorobium* spp., *Citrobacter* spp., *Clostridium* spp., *Corynebacterium* spp., *Coxiella* spp., *Deinococcus* spp., *Ehrlichia* spp., *Eikenella* spp., *Enterobacter* spp., *Enterococcus* spp., *Erysipelothrix* spp., *Escherichia* spp., *Francisella* spp., *Fusobacterium* spp., *Gardnerella* spp., *Gemella* spp., *Haemophilus* spp., *Heliobacter* spp., *Kingella* spp., *Kitasatospora* spp., *Klebsiella* spp., *Lactobacillus* spp., *Legionella* spp., *Leptospira* spp., *Listeria* spp., *Mannheimia* spp., *Mesorhizobium* spp., *Moraxella* spp., *Morganella* spp., *Mycobacterium* spp., *Mycoplasma* spp., *Neisseria* spp., *Neorickettsia* spp., *Nitrosomonas* spp., *Nocardia* spp., *Oceanobacillus* spp., *Orientia* spp., *Paracoccus* spp., *Pasteurella* spp., *Peptostreptococcus* spp., *Plasmodium* spp., *Plesiomonas* spp., *Porphyromonas* spp., *Prevotella* spp., *Propionibacterium* spp., *Proteus* spp., *Providencia* spp., *Pseudomonas* spp., *Psychobacter* spp., *Ralstonia* spp., *Rhodobacter* spp., *Rhodococcus* spp., *Rickettsia* spp., *Salmonella* spp., *Serratia* spp., *Shewanella* spp., *Shigella* spp., *Spirillum* spp., *Staphylococcus* spp., *Stenotrophomonas* spp., *Streptobacillus* spp., *Streptococcus* spp., *Streptomyces* spp., *Synechococcus* spp., *Synechocystis* spp., *Tannerella* spp., *Thermoanaerobacter* spp., *Thermotoga* spp., *Treponema* spp., *Tropheryma* spp., *Ureaplasma* spp., *Veillonella* spp., *Vibrio* spp., *Wigglesworthia* spp., *Wolbachia* spp., *Xanthomonas* spp., *Xylella* spp., *Yersinia* spp. and/or *Zymomonas* spp.
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- Further examples of such bacteria are *Acinetobacter baumannii*, *Acinetobacter* *haemolyticus*, *Actinobacillus actinomycetemcomitans*, *Actinobacillus* *pleuropneumoniae*, *Actinomyces israelii*, *Aeromonas hydrophila*, *Agrobacterium* *tumefaciens*, *Alcaligenes xylosoxidans*, *Anaplasma phagocytophilum*, *Aquifex aeolicus*, *Bacillus anthracis*, *Bacillus cereus*, *Bacillus halodurans*, *Bacillus subtilis*, *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bartonella bacilliformis*, *Bartonella henselae*, *Bifidobacterium longum*, *Bordetella bronchiseptica*, *Bordetella pertussis*, *Borrelia*
- 30
- 35

- burgdorferi, *Borrelia recurrentis*, *Bradyrhizobium japonicum*, *Branhamella catarrhalis*, *Brucella abortus*, *Brucella canis*, *Brucella melitensis*, *Brucella suis*, *Buchnera aphidicola*, *Burkholderia cepacia*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Campylobacter fetus*, *Campylobacter jejuni*, *Capnocytophaga granulosa*,
- 5 *Capnocytophaga haemolytica*, *Cardiobacterium hominis*, *Caulobacter crescentus*, *Caulobacter vibrioides*, *Chlamydia muridarum*, *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Chlamydomphila caviae*, *Chlamydomphila pneumoniae*, *Chlamydomphila psittaci*, *Chlorobium tepidum*, *Citrobacter freundii*, *Clostridium acetobutylicum*, *Clostridium botulinum*, *Clostridium difficile*, *Clostridium novyi*,
- 10 *Clostridium perfringens*, *Clostridium tetani*, *Corynebacterium diphtheriae*, *Corynebacterium efficiens*, *Corynebacterium glutamicum*, *Coxiella burnetii*, *Deinococcus radiodurans*, *Ehrlichia canis*, *Ehrlichia chaffensis*, *Eikenella corrodens*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Enterococcus faecium*, *Erysipelothrix rhusiopathiae*, *Escherichia coli*, *Escherichia coli* O157:H7, *Francisella tularensis*,
- 15 *Francisella tularensis tularensis*, *Fusobacterium necrophorum*, *Fusobacterium nucleatum*, *Gardnerella vaginalis*, *Gemella morbillorum*, *Haemophilus ducreyi*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Helicobacter pylori*, *Kingella kingii*, *Kitasatospora griseola*, *Klebsiella aerogenes*, *Klebsiella granulomatis*, *Klebsiella pneumoniae*, *Klebsiella pneumoniae ozaenae*, *Klebsiella pneumoniae pneumoniae*,
- 20 *Klebsiella pneumoniae rhinoscleromatis*, *Lactobacillus avarius*, *Lactobacillus plantarum*, *Legionella pneumophila*, *Leptospira interrogans*, *Leptospira noguchii*, *Listeria innocua*, *Listeria ivanovii*, *Listeria ivanovii ivanovii*, *Listeria monocytogenes*, *Mannheimia haemolytica*, *Mesorhizobium loti*, *Moraxella catarrhalis*, *Morganella morganii morganii*, *Mycobacterium abscessus*, *Mycobacterium africanum*,
- 25 *Mycobacterium avium*, *Mycobacterium avium paratuberculosis*, *Mycobacterium bovis*, *Mycobacterium bovis bovis*, *Mycobacterium bovis caprae*, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium intracellulare*, *Mycobacterium kansasii*, *Mycobacterium leprae*, *Mycobacterium malmoense*, *Mycobacterium marinum*, *Mycobacterium scrofulaceum*, *Mycobacterium smegmatis*, *Mycobacterium*
- 30 *tuberculosis*, *Mycobacterium ulcerans*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Mycoplasma penetrans*, *Mycoplasma pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Neorickettsia sennetsu*, *Nitrosomonas europaea*, *Nocardia arthritis*, *Nocardia asteroides*, *Nocardia cyriacigeorgica*, *Oceanobacillus iheyensis*, *Orientia tsutsugamushi*, *Paracoccus zeaxanthinifaciens*, *Pasteurella haemolytica*, *Pasteurella*
- 35 *multocida*, *Peptostreptococcus parvulus*, *Peptostreptococcus tetradius*,

- Peptostreptococcus vaginalis, Plesiomonas shigelloides, Porphyromonas gingivalis, Prevotella intermedia, Prevotella melaninogenica, Propionibacterium acnes, Proteus mirabilis, Proteus vulgaris, Providencia alcalifaciens, Providencia fredericiana, Pseudomonas aeruginosa, Pseudomonas alcaligenes, Pseudomonas fluorescens,
- 5 Pseudomonas putida, Pseudomonas stutzeri, Pseudomonas syringae, Ralstonia solanacearum, Rhodobacter capsulatus, Rhodococcus equi, Rickettsia akari, Rickettsia prowazekii, Rickettsia rickettsii, Rickettsia typhi, Salmonella choleraesuis, Salmonella enterica, Salmonella enteritidis, Salmonella paratyphi, Salmonella typhi, Salmonella typhimurium, Serratia marcescens, Shewanella oneidensis, Shewanella putrefaciens,
- 10 Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Sinorhizobium meliloti (Rhizobium meliloti), Spirillum minus, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hemolyticus, Staphylococcus saprophyticus, Stenotrophomonas maltophilia, Streptobacillus moniliformis, Streptococcus agalactiae, Streptococcus faecalis, Streptococcus milleri, Streptococcus mutans, Streptococcus
- 15 pneumoniae, Streptococcus pyogenes, Streptococcus salivarius, Streptococcus viridans, Streptomyces avermitilis, Streptomyces coelicolor, Streptomyces hygroscopicus, Streptomyces lividans, Streptomyces rishiriensis, Synechococcus elongates, Synechococcus leopoliensis, Tannerella forsythensis, Thermoanaerobacter tengcongensis, Thermotoga maritime, Treponema carateum,
- 20 Treponema denticola, Treponema endemicum, Treponema pallidum, Treponema petenue, Tropheryma whipplei, Ureaplasma urealyticum, Veillonella alcalescens alcalescens, Veillonella parvula atypica, Vibrio cholerae, Vibrio parahemolyticus, Vibrio vulnificus, Wigglesworthia glossinidia, Xanthomonas axonopodis, Xanthomonas campestris, Xanthomonas maltophilia, Xylella fastidiosa, Yersinia enterocolitica,
- 25 Yersinia pestis, Yersinia pseudotuberculosis and/or Zymomonas mobilis.

The classification of bacteria into "gram-positive", "gram-negative" or "bacteria that are difficult to Gram stain (atypical)" as well as the determination of the aerobic or anaerobic state can be easily performed by the skilled artisan on the basis of his expert knowledge, e.g. by appropriate staining and metabolic assays which represent only

30 routine experimentation.

In this connection the term "gram-negative" in the course of the present invention is intended to comprise bacteria that cannot be Gram stained as well as those that are difficult to Gram stain (atypical). In contrast, the term "gram-positive" in connection with bacteria is intended for the purpose of the present invention to comprise all bacteria

35 that can be Gram stained and/or are known to be gram-positive.

The term "fungus" or "fungi" is intended to comprise all known single-cell/unicellular and/or multi-cellular members of the kingdom of fungi, such as Chytridiomycota, Zygomycota, Glomeromycota, Ascomycota and/or Basidiomycota, as well as in
 5 addition Myxomycota, Oomycota and/or Hypochytriomycota.

Examples of such fungi are Absidia spp., Acremonium spp., Alternaria spp., Aspergillus spp., Bipolaris spp., Candida spp., Cladophialophora spp., Cladosporium spp., Coccidioides spp., Coniothyrium spp., Cryptococcus spp., Cunninghamella spp., Curvularia spp., Epidermophyton spp., Exophiala spp., Exserohilum spp., Fonsecaea
 10 spp., Fusarium spp., Histoplasma spp., Lacazia spp., Lasiodiplodia spp., Leptosphaeria spp., Madurella spp., Microsporum spp., Mucor spp., Mucorales spp., Neotestudina spp., Ochroconis spp., Onychocola spp., Paecilomyces spp., Paracoccidioides spp., Penicillium spp., Phialophora spp., Pseudallesheria spp., Pyrenochaeta spp., Rhizomucor spp., Rhizopus spp., Scedosporium spp., Scopulariopsis spp., Scytalidium
 15 spp., Sporothrix spp., Trichophyton spp. and/or Wangiella spp.

Further examples of such fungi are Absidia corymbifera, Acremonium falciforme, Acremonium recifei, Aspergillus flavus, Aspergillus fumigatus, Aspergillus glaucus, Aspergillus nidulans, Aspergillus niger, Aspergillus terreus, Bipolaris australiensis, Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis, Candida
 20 tropicalis, Cladophialophora bantiana, Cladophialophora carrionii, Coccidioides immitis, Coniothyrium fuckelii, Cryptococcus gattii, Cryptococcus neoformans, Cunninghamella bertholletiae, Epidermophyton floccosum, Exophiala jeanselmei, Exophiala spinifera, Fonsecaea compacta, Fonsecaea pedrosoi, Fusarium oxysporum, Fusarium solani, Histoplasma capsulatum capsulatum, Histoplasma capsulatum duboisii, Lacazia loyai,
 25 Lasiodiplodia theobromae, Leptosphaeria senegalensis, Madurella grisea, Madurella mycetomatis, Microsporum audouinii, Microsporum canis, Microsporum gypseum, Neotestudina rosatii, Ochroconis gallopava, Onychocola Canadensis, Paecilomyces lilacinus, Paracoccidioides brasiliensis, Phialophora parasitica, Phialophora repens, Phialophora verrucosa, Pseudallesheria boydii, Pyrenochaeta romeroi, Rhizomucor
 30 pusillus, Rhizopus arrhizus, Rhizopus oryzae, Scedosporium apiospermum, Scedosporium inflatum, Scedosporium prolificans, Scopulariopsis brevicaulis, Scytalidium dimidiatum, Sporothrix schenckii, Trichophyton mentagrophytes, Trichophyton rubrum, Trichophyton schoenleinii, Trichophyton tonsurans and/or Wangiella dermatitidis.

The term "protozoon" or "protozoa" is intended to comprise all known single-cell/unicellular and/or multi-cellular members of Sporozoa, Gregarinida, Coccida, Piroplasmida, Babesia, Microsporidia, Giardiinae, Trichomonadida, Diplomonadida, 5 Hypermastigida, Trypanosoma, Entamoebidae, Kinetoplasta, Tryposomatidea, Tryposomatidae, Apicomplexa, Haemosporida, Plasmodiidae, Rhizopoda and/or Amoebina.

Examples of such protozoa are Acanthamoeba spp., Amoeba spp., Babesia spp., Balantidium spp., Cryptosporidium spp., Cyclospora spp., Dientamoeba spp., 10 Echinamoeba spp., Endolimax spp., Entamoeba spp., Enterocytozoon spp., Giardia spp., Hartmanella spp., Isospora spp., Jodamoeba spp., Lamblia spp., Leishmania spp., Microsporidium spp., Naegleria spp., Nosema spp., Paramecium spp., Paramoeba spp., Penumocystis spp., Plasmodium spp., Sarcocystis spp., Tetrahymena spp., Toxoplasma spp., Trichomonas spp. and/or Trypanosoma spp.

15 Further examples of such protozoa are Amoeba proteus, Babesia microti, Balantidium coli, Cryptosporidium parvum, Cyclospora cayetanensis, Dientamoeba fragilis, Endolimax nana, Entamoeba coli, Entamoeba gingivalis, Entamoeba hartmanni, Entamoeba histolytica, Enterocytozoon bienersi, Enterocytozoon cuniculi, Giardia lamblia, Giardia lamblia intestinalis, Isospora belli, Jodamoeba bütschlii, 20 Lamblia intestinalis, Leishmania braziliensis braziliensis, Leishmania chagasi, Leishmania donovani, Leishmania infantum, Leishmania major, Leishmania mexicana, Leishmania mexicana amazonensis, Leishmania mexicana mexicana, Leishmania tropica, Leishmania Viannia, Leishmania Viannia braziliensis, Leishmania Viannia guyanensis, Leishmania Viannia panamensis, Leishmania Viannia peruviana, 25 Naegleria fowleri, Nosema corneum, Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, Plasmodium vivax, Pneumocystis carinii, Sarcocystis bovis, Sarcocystis hominis, Tetrahymena pyriformis, Toxoplasma gondii, Trichomonas vaginalis, Trypanosoma brucei, Trypanosoma brucei brucei, Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense, Trypanosoma cruzi, Trypanosoma cruzi 30 cruzi, Trypanosoma cruzi marinkellei, Trypanosoma equinum, Trypanosoma equiperdum, Trypanosoma evansi, Trypanosoma theileri and/or Trypanosoma vivax.

The term "virus" or "viruses" is intended to comprise all known DNA viruses, e.g. dsDNA viruses (double stranded DNA) and ssDNA viruses (single stranded DNA);

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RNA viruses, e.g. dsRNA viruses (double stranded RNA), (+)ssRNA viruses (positive single stranded RNA or mRNA like) and (-)ssRNA viruses (negative single-stranded RNA); as well as DNA and RNA reverse transcribing viruses (retroviruses), e.g. ssRNA-RT viruses (single stranded RNA) and dsDNA-RT viruses (double stranded
5 DNA). These can be either coated or uncoated.

Examples of such viruses are Caudovirales, Myoviridae, Podoviridae, Siphoviridae, Ascoviridae, Adenoviridae, Asfiviridae, Baculoviridae, Corticoviridae, Fuselloviridae, Guttaviridae, Herpesviridae, Iridoviridae, Lipothrixviridae, Nimaviridae, Papillomaviridae, Phycodnaviridae, Plasmaviridae, Polyomaviridae, Poxviridae,
10 Rudiviridae, Tectiviridae, Inoviridae, Microviridae, Geminiviridae, Circoviridae, Nanoviridae, Parvoviridae, Anellovirus, Birnaviridae, Chrysoviridae, Cystoviridae, Hypoviridae, Partitiviridae, Reoviridae, Totiviridae, Endornavirus, Nidovirales, Arteriviridae, Coronaviridae, Roniviridae, Astroviridae, Barnaviridae, Bromoviridae, Caliciviridae, Closteroviridae, Comoviridae, Dicistroviridae, Flaviviridae, Flexiviridae,
15 Hepeviridae, Leviviridae, Luteoviridae, Marnaviridae, Namaviridae, Nodaviridae, Picomaviridae, Potyviridae, Sequiviridae, Tetraviridae, Togaviridae, Tombusviridae, Tymoviridae, Benyvirus, Cheravirus, Furovirus, Hordeivirus, Idaeovirus, Machlomovirus, Ourmiavirus, Pecluvirus, Pomovirus, Sadwavirus, Sobemovirus, Tobamovirus, Tobravirus, Umbravirus, Mononegavirales, Bornaviridae, Filoviridae,
20 Paramyxoviridae, Rhabdoviridae, Arenaviridae, Bunyaviridae, Orthomyxoviridae, Deltavirus, Ophiovirus, Tenuivirus, Varicosavirus, Metaviridae, Pseudoviridae, Retroviridae, Hepadnaviridae and/or Caulimoviridae.

Further examples of such viruses are adenovirus type 1, 2, 3, 5, 11, 21, adenovirus, alphavirus, arbovirus, arenavirus, borna disease virus, bunyavirus,
25 calicivirus, California encephalitis virus, Colorado tick fever virus, coronavirus cowpox virus, coxsackie type A virus, coxsackie type B virus, coxsackie virus type A-16, A-24, Coxsackie virus type B1, B2, B3, B4, B5, cytomegalovirus (CMV), deltavirus, dengue virus, Ebola virus, echovirus, EEE virus, enterovirus type 7, 70, Epstein-Barr virus (EBV), filovirus, flavivirus, foot and mouth disease virus, FSME virus, hantavirus type
30 Hantaan, Seoul, Dobrava (Belgrade), Puumala, Sin Nombre, Black Creek Canal, Bayou, New York-1, hantavirus, hepadnavirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, hepatitis F virus, hepatitis G virus, herpes simplex virus (HSV), herpes simplex virus type 1 and 2 (HSV-1, HSV-2), herpesvirus, HIV, HIV-1, HIV-2, human papilloma virus (HPV), human T cell leukemia
35 virus, human T-cell lymphotropic virus type I and II (HTLV-I, -II), influenza virus,

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influenza virus type A (H5N1) and (H3N2), influenza virus type A, B, C, Japanese encephalitis virus, JC virus, juninvirus, Kaposi's sarcoma-associated virus, LaCross virus, Lassavirus, lentivirus, lymphocytic choriomeningitis virus, machupovirus, Marburg virus, measles virus, Molluscum virus, mumps virus, Norwalk virus, orfivirus, orthomyxovirus, papovavirus, parainfluenza virus type 1, 2, 3, parainfluenza virus, paramyxovirus type 1, 2, 3, 4, paramyxovirus, parvovirus B19, parvovirus, picornavirus, poliovirus, poxvirus, rabies virus, Rabies virus, reovirus, respiratory syncytial virus, rhabdovirus, rhinoviruses, rotavirus, Rubella virus, rubeola virus, rubivirus, SARS virus, Simian virus 40, SLE virus, togavirus, Torque teno virus, vaccinia virus, varicella zoster virus, variola virus, Vicia faba endornavirus, WEE virus, West Nile virus and/or Yellow fever virus.

The term "spp." in connection with any microorganism is intended to comprise for the purpose of the present invention all members of a given genus, including species, subspecies and others. The term "Trypanosoma spp." for instance is intended to comprise all members of the genus Trypanosoma, such as Trypanosoma cruzi, Trypanosoma brucei, Trypanosoma brucei brucei and Trypanosoma brucei gambiense.

For the purpose of the present invention, the term "treatment" is also intended to include prophylactic treatment or alleviation.

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In a preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a bacterium.

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In another preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a gram-positive bacterium.

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In yet another preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases

and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a gram-negative bacterium.

More preferably, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a bacterium, preferably a gram-positive bacterium or a gram-negative bacterium, and selected from the group consisting of "Acinetobacter spp., Actinobacillus spp., Actinomyces spp., Aeromonas spp., Agrobacterium spp., Alcaligenes spp., Anaplasma spp., Aquifex spp., Bacillus spp., Bacteroides spp., Bifidobacterium spp., Bordetella spp., Borrelia spp., Bradyrhizobium spp., Branhamella spp., Brucella spp., Buchnera spp., Burkholderia spp., Campylobacter spp., Capnocytophaga spp., Cardiobacterium spp., Caulobacter spp., Chlamydia spp., Chlamydophila spp., Chlorobium spp., Citrobacter spp., Clostridium spp., Corynebacterium spp., Coxiella spp., Deinococcus spp., Ehrlichia spp., Eikenella spp., Enterobacter spp., Enterococcus spp., Erysipelothrix spp., Escherichia spp., Francisella spp., Fusobacterium spp., Gardnerella spp., Gemella spp., Haemophilus spp., Heliobacter spp., Kingella spp., Kitasatospora spp., Klebsiella spp., Lactobacillus spp., Legionella spp., Leptospira spp., Listeria spp., Mannheimia spp., Mesorhizobium spp., Moraxella spp., Morganella spp., Mycobacterium spp., Mycoplasma spp., Neisseria spp., Neorickettsia spp., Nitrosomonas spp., Nocardia spp., Oceanobacillus spp., Orientia spp., Paracoccus spp., Pasteurella spp., Peptostreptococcus spp., Plesiomonas spp., Porphyromonas spp., Prevotella spp., Propionibacterium spp., Proteus spp., Providencia spp., Pseudomonas spp., Psychobacter spp., Ralstonia spp., Rhodobacter spp., Rhodococcus spp., Rickettsia spp., Salmonella spp., Serratia spp., Shewanella spp., Shigella spp., Spirillum spp., Staphylococcus spp., Stenotrophomonas spp., Streptobacillus spp., Streptococcus spp., Streptomyces spp., Synechococcus spp., Synechocystis spp., Tannerella spp., Thermoanaerobacter spp., Thermotoga spp., Treponema spp., Tropheryma spp., Ureaplasma spp., Veillonella spp., Vibrio spp., Wigglesworthia spp., Wolbachia spp., Xanthomonas spp., Xylella spp., Yersinia spp. and/or Zymomonas spp."

Even more preferably, the bacterium is selected from the group consisting of "Bacteroides spp., Branhamella spp., Chlamydia spp., Escherichia spp., Haemophilus spp., Klebsiella spp., Mycobacterium spp., Mycoplasma spp., Proteus spp., Pseudomonas spp., Serratia spp., Staphylococcus spp. and/or Streptococcus spp."

- Most preferably, the bacterium is selected from the group consisting of "Bacteroides fragilis, Branhamella catarrhalis, Chlamydia pneumoniae, Chlamydia psittaci, Chlamydia trachomatis, Escherichia coli, Haemophilus ducreyi, Haemophilus influenzae, Haemophilus parainfluenzae, Haemophilus ducreyi, Klebsiella
- 5 granulomatis, Klebsiella pneumoniae, Klebsiella pneumoniae ozaenae, Klebsiella pneumoniae pneumoniae, Klebsiella pneumoniae rhinoscleromatis, Mycobacterium africanum, Mycobacterium avium, Mycobacterium avium paratuberculosis, Mycobacterium bovis, Mycobacterium bovis bovis, Mycobacterium bovis caprae, Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium intracellulare,
- 10 Mycobacterium kansasii, Mycobacterium leprae, Mycobacterium malmoeense, Mycobacterium marinum, Mycobacterium scrofulaceum, Mycobacterium tuberculosis, Mycobacterium ulcerans, Mycoplasma genitalium, Mycoplasma hominis, Mycoplasma pneumoniae, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas alcaligenes, Pseudomonas fluorescens, Pseudomonas putida,
- 15 Pseudomonas stutzeri, Serratia marcescens, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hemolyticus, Staphylococcus saprophyticus, Streptococcus agalactiae, Streptococcus faecalis, Streptococcus milleri, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus salivarius and/or Streptococcus viridans".
- 20 In an even more preferred embodiment, the compounds of the invention are bactericidal (bacteria-killing) and/or bacteriostatic (bacterial growth/reproduction inhibiting). In this context, the compounds of the invention can even be bactericidal to one or more certain bacterial geni, species, subspecies, strains etc. but only bacteriostatic to another or further bacterial geni, species, subspecies, strains etc. and
- 25 vice versa.

- In another preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where
- 30 the microorganism is a bacterium, preferably a gram-positive bacterium or a gram-negative bacterium, more preferably the different preferred bacteria as illustrated herein, where the compounds of the invention are preferably bactericidal (bacteria-killing) and/or bacteriostatic (bacterial growth/reproduction inhibiting), where the alkyl phospholipid derivative is selected from the herein generically or explicitly disclosed

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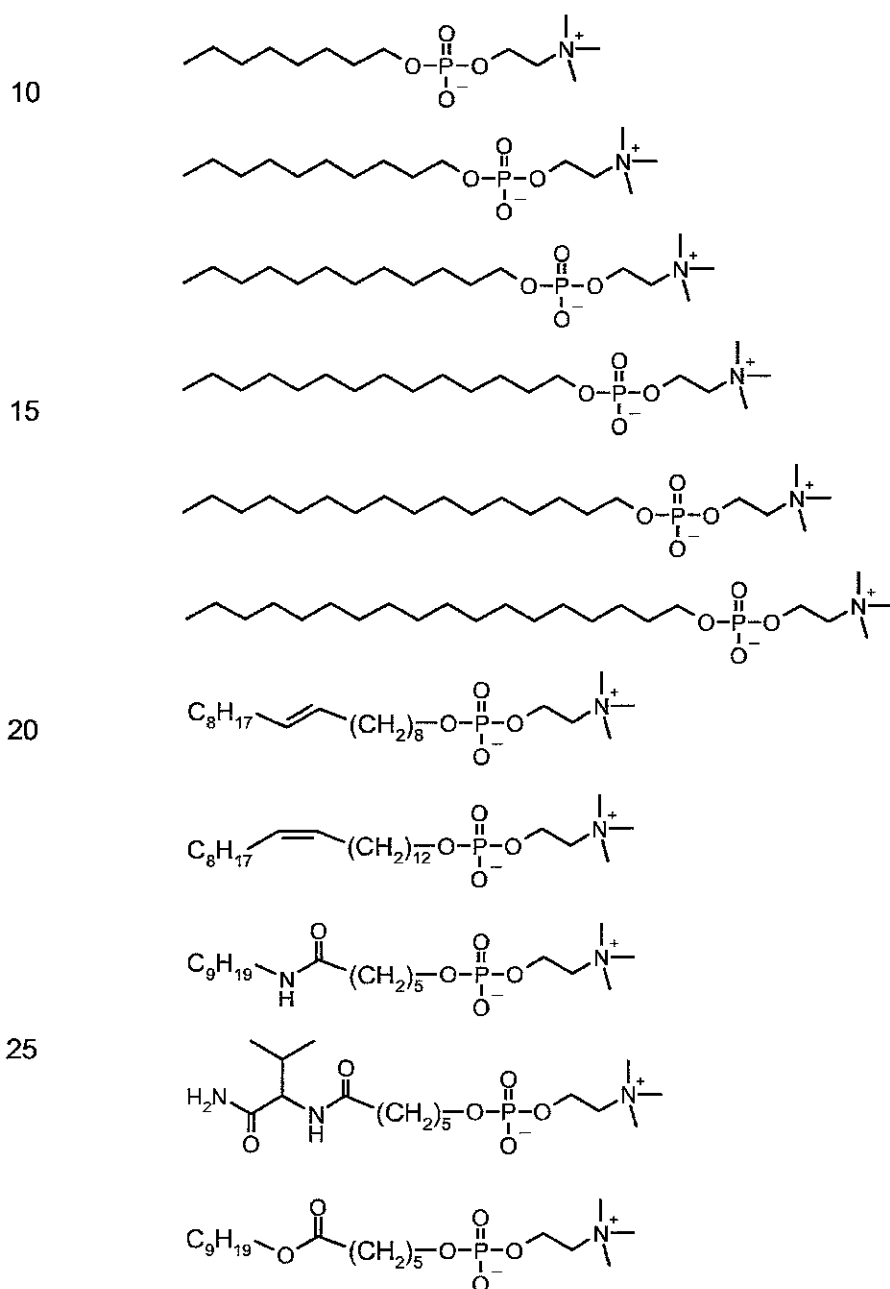
alkyl phospholipid derivatives according to formula (I), including preferred subsets of formula (I) and Compounds 1 to 317,

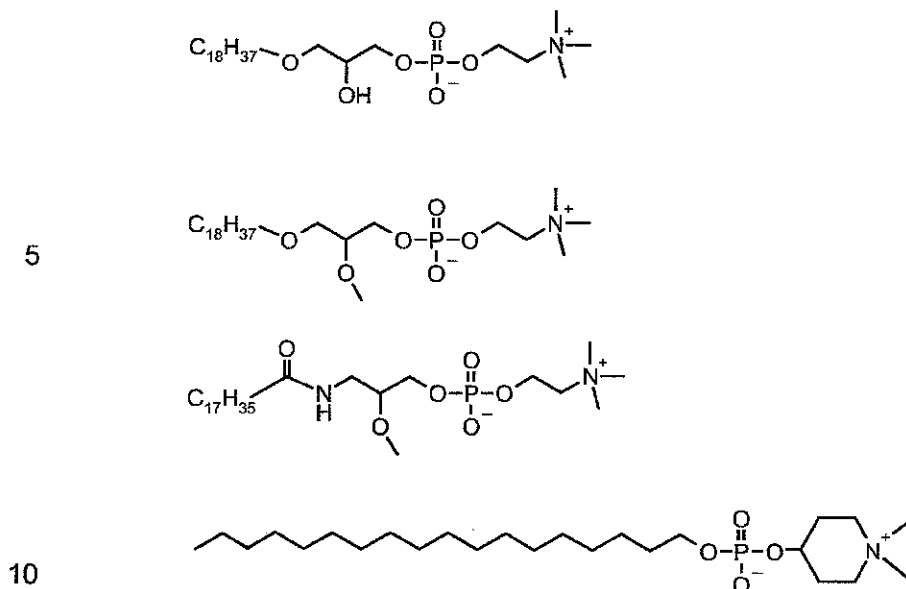
with the proviso that if R8 is “-VR9R10R11”, V is a nitrogen atom,

with the further proviso that if R8 is “substituted or unsubstituted heterocycle”,

5 “substituted or unsubstituted heterocycle” does not contain one or more arsenic atoms and does not contain one or more quaternary arsenic atoms,

and with the further proviso that the following compounds are excluded from formula (I), including preferred subsets of formula (I) and Compounds 1 to 317:





Even more preferably, for above presented uses against bacteria the alkyl
 15 phospholipid derivative is selected from the group consisting of: **"Compound 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 34, 37, 38, 62, 66, 67, 89, 90, 107, 117, 144, 260, 266, 301, 307 and/or compound 314"**.

In a further preferred embodiment, the compounds of the invention can be used for
 20 the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a fungus and selected from the group consisting of "Absidia spp., Acremonium spp., Alternaria spp., Aspergillus spp., Bipolaris spp., Candida spp., Cladophialophora spp., Cladosporium spp., Coccidioides spp., Coniothyrium spp.,
 25 Cryptococcus spp., Cunninghamella spp., Curvularia spp., Epidermophyton spp., Exophiala spp., Exserohilum spp., Fonsecaea spp., Fusarium spp., Histoplasma spp., Lacazia spp., Lasiodiplodia spp., Leptosphaeria spp., Madurella spp., Microsporum spp., Mucor spp., Mucorales spp., Neotestudina spp., Ochroconis spp., Onychocola spp., Paecilomyces spp., Paracoccidioides spp., Penicillium spp., Phialophora spp.,
 30 Pseudallesheria spp., Pyrenochaeta spp., Rhizomucor spp., Rhizopus spp.,

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Scedosporium spp., Scopulariopsis spp., Scytalidium spp., Sporothrix spp., Trichophyton spp. and/or Wangiella spp.” More preferably, the fungus is selected from the group consisting of “Absidia spp., Aspergillus spp., Bipolaris spp., Candida spp., Cryptococcus spp., Cunninghamella spp., Exophiala spp., Fusarium spp.,
 5 Paecilomyces spp., Rhizopus spp. and/or Scedosporium spp.” Most preferably, the fungus is selected from the group consisting of “Absidia corymbifera, Aspergillus flavus, Aspergillus fumigatus, Aspergillus terreus, Bipolaris australiensis, Candida albicans, Candida glabrata, Candida krusei, Candida parapsilosis, Candida tropicalis, Cryptococcus gattii, Cryptococcus neoformans, Cunninghamella bertholletiae,
 10 Exophiala jeanselmei, Exophiala spinifera, Fusarium solani, Paecilomyces lilacinus, Rhizopus oryzae, Scedosporium apiospermum and/or Scedosporium prolificans. Even more preferably, the alkyl phospholipid derivative is selected from the group consisting of: **“Compound 1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 18, 19 20 and/or compound 22”**.

15

In another preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a protozoon and selected from the group consisting of
 20 “Acanthamoeba spp., Amoeba spp., Babesia spp., Balantidium spp., Cryptosporidium spp., Cyclospora spp., Dientamoeba spp., Echinamoeba spp., Endolimax spp., Entamoeba spp., Enterocytozoon spp., Giardia spp., Hartmanella spp., Isospora spp., Jodamoeba spp., Lamblia spp., Leishmania spp., Microsporidium spp., Naegleria spp., Nosema spp., Paramecium spp., Paramoeba spp., Penumocystis spp., Plasmodium
 25 spp., Sarcocystis spp., Tetrahymena spp., Toxoplasma spp., Trichomonas spp. and/or Trypanosoma spp.”. More preferably, the protozoon is selected from the group consisting of “Leishmania spp., Plasmodium spp., Toxoplasma spp. and/or Trypanosoma spp.” Most preferably, the protozoon is selected from the group consisting of “Leishmania braziliensis braziliensis, Leishmania chagasi, Leishmania
 30 donovani, Leishmania infantum, Leishmania major, Leishmania mexicana, Leishmania mexicana amazonensis, Leishmania mexicana mexicana, Leishmania tropica, Leishmania Viannia, Leishmania Viannia braziliensis, Leishmania Viannia guyanensis, Leishmania Viannia panamensis, Leishmania Viannia peruviana, Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale, Plasmodium vivax, Toxoplasma
 35 gondii, Trypanosoma brucei, Trypanosoma brucei brucei, Trypanosoma brucei

gambiense, Trypanosoma brucei rhodesiense, Trypanosoma cruzi, Trypanosoma cruzi cruzi, Trypanosoma cruzi marinkellei, Trypanosoma equinum, Trypanosoma equiperdum, Trypanosoma evansi, Trypanosoma theileri and/or Trypanosoma vivax". Even more preferably, the alkyl phospholipid derivative is selected from the group consisting of: "Compound 1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 18, 19 and/or compound 20".

In another preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a virus and selected from the group consisting of "DNA virus; dsDNA virus, ssDNA virus; RNA virus; dsRNA virus; (+)ssRNA virus; (-)ssRNA virus; DNA/RNA reverse transcribing virus; ssRNA-RT virus and/or dsDNA-RT virus". More preferably, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the microorganism is a virus and selected from the group consisting of "adenovirus type 1, 2, 3, 5, 11, 21, adenovirus, alphavirus, arbovirus, arenavirus, borna disease virus, bunyavirus, calicivirus, California encephalitis virus, Colorado tick fever virus, coronavirus cowpox virus, coxsackie type A virus, coxsackie type B virus, coxsackie virus type A-16, A-24, Coxsackie virus type B1, B2, B3, B4, B5, cytomegalovirus (CMV), deltavirus, dengue virus, Ebola virus, echovirus, EEE virus, enterovirus type 7, 70, Epstein-Barr virus (EBV), filovirus, flavivirus, foot and mouth disease virus, FSME virus, hantavirus type Hantaan, Seoul, Dobrava (Belgrade), Puumala, Sin Nombre, Black Creek Canal, Bayou, New York-1, hantavirus, hepadnavirus, hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, hepatitis F virus, hepatitis G virus, herpes simplex virus (HSV), herpes simplex virus type 1 and 2 (HSV-1, HSV-2), herpesvirus, HIV, HIV-1, HIV-2, human papilloma virus (HPV), human T cell leukemia virus, human T-cell lymphotropic virus type I and II (HTLV-I, -II), influenza virus, influenza virus type A (H5N1) and (H3N2), influenza virus type A, B, C, Japanese encephalitis virus, JC virus, juninivirus, Kaposi's sarcoma-associated virus, LaCross virus, Lassavirus, lentivirus, lymphocytic choriomeningitis virus, machupovirus, Marburg virus, measles virus, Molluscum virus, mumps virus, Norwalk virus, orfivirus, orthomyxovirus, papovavirus, parainfluenza virus type 1, 2, 3, parainfluenza virus, paramyxovirus type 1, 2, 3, 4, paramyxovirus, parvovirus B19, parvovirus, picornavirus,

poliovirus, poxvirus, rabies virus, Rabies virus, reovirus, respiratory syncytial virus, rhabdovirus, rhinoviruses, rotavirus, Rubella virus, rubeola virus, rubivirus, SARS virus, Simian virus 40, SLE virus, togavirus, Torque teno virus, vaccinia virus, varicella zoster virus, variola virus, Vicia faba endornavirus, WEE virus, West Nile virus and/or Yellow fever virus". Even more preferably, the alkyl phospholipid derivative is selected from the group consisting of: "**Compound 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 18, 19 and/or compound 20**".

All stereoisomers of the compounds of the invention are contemplated, either in a mixture or in pure or substantially pure form. The compounds of the invention can have asymmetric centers at any of the carbon atoms. Consequently, they can exist in the form of their racemates, in the form of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers. The mixtures may have any desired mixing ratio of the stereoisomers.

Thus, for example, the compounds of the invention which have one or more centers of chirality and which occur as racemates or as diastereomer mixtures can be fractionated by methods known per se into their optical pure isomers, i.e. enantiomers or diastereomers. The separation of the compounds of the invention can take place by column separation on chiral or nonchiral phases or by recrystallization from an optionally optically active solvent or with use of an optically active acid or base or by derivatization with an optically active reagent such as, for example, an optically active alcohol, and subsequent elimination of the radical.

The compounds of the invention may be present in the form of their double bond isomers as "pure" E or Z isomers, or in the form of mixtures of these double bond isomers.

Where possible, the compounds of the invention may be in the form of the tautomers.

It is likewise possible for the compounds of the invention to be in the form of any desired prodrugs such as, for example, esters, carbonates, carbamates, ureas, amides or phosphates, in which cases the actually biologically active form is released only through metabolism. Any compound that can be converted in vivo to provide the bioactive agent (i.e. compounds of the invention) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art and are described for instance in:

- (i) Wermuth CG et al., Chapter 31: 671-696, The Practice of Medicinal Chemistry, Academic Press 1996;
- 5 (ii) Bundgaard H, Design of Prodrugs, Elsevier 1985; and
- (iii) Bundgaard H, Chapter 5: 131-191, A Textbook of Drug Design and Development, Harwood Academic Publishers 1991.

Said references are incorporated herein by reference.

It is further known that chemical substances are converted in the body into
10 metabolites which may where appropriate likewise elicit the desired biological effect - in some circumstances even in more pronounced form.

Any biologically active compound that was converted in vivo by metabolism from any of the compounds of the invention is a metabolite within the scope and spirit of the invention.

15

The compounds of the invention can, if they have a sufficiently basic group such as, for example, a secondary or tertiary amine, be converted with inorganic and organic acids into salts. The pharmaceutically acceptable salts of the compounds of the invention are preferably formed with hydrochloric acid, hydrobromic acid, iodic acid,
20 sulfuric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, carbonic acid, formic acid, acetic acid, sulfoacetic acid, trifluoroacetic acid, oxalic acid, malonic acid, maleic acid, succinic acid, tartaric acid, racemic acid, malic acid, embonic acid, mandelic acid, fumaric acid, lactic acid, citric acid, taurocholic acid, glutaric acid, stearic acid, glutamic acid or aspartic acid. The salts which are formed are, inter alia,
25 hydrochlorides, chlorided, hydrobromides, bromides, iodides, sulfates, phosphates, methanesulfonates, tosylates, carbonates, bicarbonates, formates, acetates, sulfoacetates, triflates, oxalates, malonates, maleates, succinates, tartrates, malates, embonates, mandelates, fumarates, lactates, citrates, glutarates, stearates, aspartates and glutamates. The stoichiometry of the salts formed from the compounds of the
30 invention may moreover be an integral or non-integral multiple of one.

The compounds of the invention can, if they contain a sufficiently acidic group such as, for example, the carboxy, sulfonic acid, phosphoric acid or a phenolic group, be converted with inorganic and organic bases into their physiologically tolerated salts.

Examples of suitable inorganic bases are ammonium, sodium hydroxide, potassium hydroxide, calcium hydroxide, and of organic bases are ethanolamine, diethanolamine, triethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, cyclohexylamine, dibenzylethylene-diamine and lysine. The stoichiometry of the salts
5 formed from the compounds of the invention can moreover be an integral or non-integral multiple of one.

It is likewise possible for the compounds of the invention to be in the form of their solvates and, in particular, hydrates which can be obtained for example by crystallization from a solvent or from aqueous solution. It is moreover possible for one,
10 two, three or any number of solvate or water molecules to combine with the compounds of the invention to give solvates and hydrates.

In a preferred embodiment, the compounds of the invention are available in the form of their hydrates, with any number of water molecules combined/complexed to them, including integer and non-integer ratios, such as 1:0,5; 1:1; 1:1,5; 1:2; 1:2,5; 1:3;
15 1:3,5; 1:4 etc.

It is known that chemical substances form solids which exist in different order states which are referred to as polymorphic forms or modifications. The various modifications of a polymorphic substance may differ greatly in their physical properties. The compounds of the invention can exist in various polymorphic forms and certain
20 modifications may moreover be metastable. All these polymorphic forms of the compounds are to be regarded as belonging to the invention.

The compounds of the invention are suitable for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by
25 microorganisms, in particular where the microorganism is selected from the group consisting of "bacterium, fungus, protozoon and/or virus".

For the purpose of the present invention, all known diseases and/or pathophysiological conditions in mammals are intended to be comprised that are caused by bacteria.

30 Examples of such bacterial diseases and/or pathophysiological conditions are actinomycosis, acute epiglottitis, acute otitis media, acute purulent (septic) arthritis, acute purulent meningitis, anthrax, appendicitis, bacillary dysentery, bacteremia, black death, borderline leprosy, borreliose, botulism, breast abscesses, bronchitis,

- brucellosis, bubonic plague, carbuncles, cellulitis, cephalic tetanus, cerebritis, cervicitis, Cholera, conjunctivitis, cutaneous anthrax, cystitis, dermatitis, diarrhea, empyema, encephalitis, endocarditis, enteric fever, enteritis, enterocolitis, epididymitis, erysipelas, erysipeloethricosis, exfoliation, extrapulmonary tuberculosis, food poisoning, furuncles,
- 5 gas gangrene, gastritis, gastroenteritis, gastrointestinal tract (GI) infections, gastrointestinal tuberculosis, genitourinary tuberculosis, glomerulonephritis, hematogenous or lymphohematogenous tuberculosis, impetigo, intra-abdominal infections, laryngitis, lepromatous leprosy, leprosy, leptospirosis, listeriosis, Localized tetanus, Lyme disease, mastitis, melioidosis, meningitis, meningoencephalitis, miliary
- 10 tuberculosis, myonecrosis, nausea, necrotizing enteritis, neonatal listeriosis, neonatal sepsis, nocardiosis, ophthalmitis, osteomyelitis, osteomyelitis, otitis media, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pertussis, Pestis, pharyngitis, plague, pneumonia, postpartum sepsis, primary listeremia, proctitis, prostatitis, puerperal sepsis, pulmonary anthrax, pulmonary tuberculosis, Pustular or bullous skin subcutaneous
- 15 abscesses, pyelonephritis, pyoderma, Rabbit/Deer Fly Fever, rat-bite fever, relapsing fever, rheumatic fever, rhinitis, rhombencephalitis, salmonellosis, salpingitis, scalded skin syndrome, scarlet fever, sepsis, septic arthritis, septic thrombophlebitis, septicemia, shigellosis, sinusitis, skin infections, stitch abscesses, syphilis, tetanus, tick/recurrent/famine fever, tonsillitis, Toxic shock syndrome, tracheobronchitis,
- 20 treponematoses, tuberculosis, tuberculoid leprosy, tuberculous lymphadenitis, tuberculous meningitis, tuberculous pericarditis, tuberculous peritonitis, tularemia, typhoid fever, ulcer, undulant/Malta/ Mediterranean/Gibraltar Fever, urethritis, urinary tract infections (UTIs), vomiting and/or wound infections as well as their different forms and subforms. Preferably, diseases and/or pathophysiological conditions in mammals
- 25 that are caused by bacteria are selected from the group consisting of "acute otitis media, bronchitis, dermatitis, encephalitis, endocarditis, gastritis, gastroenteritis, gastrointestinal tract (GI) infections, laryngitis, meningitis, otitis media, pericarditis, pharyngitis, pneumonia, sepsis, sinusitis, skin infections, tuberculosis and/or urinary tract infections (UTIs) as well as their different forms and subforms".
- 30 For the purpose of the present invention, all known diseases and/or pathophysiological conditions in mammals are intended to be comprised that are caused by fungi.

Examples of such fungal diseases and/or pathophysiological conditions are aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis,

35 cryptococcosis, dermatomycosis, dermatophytosis, histoplasmosis, lobomycosis,

5 mucormycosis, mycetoma, mycotic keratitis, oculomycosis, onychomycosis, otomycosis, paracoccidiomycosis, phaeohyphomycosis, piedra, pityriasis versicolor, rhinosporidiosis, sporotrichosis, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea favosa, tinea nigra, tinea pedis, tinea unguium and/or zygomycosis as well as their different forms and subforms.

For the purpose of the present invention, all known diseases and/or pathophysiological conditions in mammals are intended to be comprised that are caused by protozoa.

10 Examples of such protozoal diseases and/or pathophysiological conditions are African trypanosomiasis, American trypanosomiasis, amoebiasis, amoebic dysentery, amoebic keratitis, amoebic meningoencephalitis, amoebic vaginitis, babesiosis, chagas disease, coccidiosis, cryptosporidiosis, cutaneous leishmaniasis, cyclosporiasis, dientamoebiasis, entamoebiasis, giardiasis, isosporiasis, lambliasis, leishmaniasis, malaria, malaria quartana, malaria tertiana, malaria tropica, microsporidiosis, 15 mucocutaneous leishmaniasis, pneumocystosis, sarcosporidiosis, sleeping sickness, toxoplasmosis, trichomoniasis, trypanosomiasis and/or visceral leishmaniasis as well as their different forms and subforms. Preferably, diseases and/or pathophysiological conditions in mammals that are caused by protozoa are selected from the group consisting of "trypanosomiasis, American trypanosomiasis, chagas disease, 20 leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis, malaria, malaria tropica and/or toxoplasmosis as well as their different forms and subforms".

For the purpose of the present invention, all known diseases and/or pathophysiological conditions in mammals are intended to be comprised that are 25 caused by viruses.

Examples of such viral diseases and/or pathophysiological conditions are acute febrile respiratory disease (AFRD), acute hemorrhagic conjunctivitis, acute hemorrhagic cystitis, acute pharyngoconjunctival fever (APC), acute posterior ganglionitis, acute respiratory disease (ARD), AIDS, arbovirus encephalitis, aseptic 30 meningitis, borna disease, Bornholm disease (pleurodynia), breakbone/dandy fever, bronchiolitis, bronchitis, Burkitt's lymphoma, California encephalitis, Castleman's disease, cervical cancer, chickenpox, Chikungunya disease, Colorado tick fever, common cold, conjunctivitis, Cowpox, Creutzfeldt-Jakob disease, Croup, cytomegalic inclusion disease, dengue, dengue hemorrhagic fever, Devil's grip (pleurodynia),

Eastern equine encephalitis, Ebola hemorrhagic fever, Ebola virus infection, encephalomyelitis, epidemic keratoconjunctivitis (EKC), epidemic nephrosonephritis, erythema infectiosum, fatal familial insomnia, fifth disease, flue, foot and mouth disease (hand-foot-mouth disease), gastroenteritis, geniculate zoster, genital herpes, genital warts, German measles, Gerstmann-Sträussler-Scheinker disease, gingivostomatitis, Hantaan-Korean hemorrhagic fever, hantavirus hemorrhagic fever, hantavirus pulmonary syndrome (HPS), hemorrhagic fever with renal syndrome (HFRS), hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, herpangina, herpes labialis, herpes zoster, herpetic stomatitis, HIV infection, Hodgkin's disease, HTLV-I-associated myelopathy, hydrophobia, infectious myocarditis, infectious pericarditis, influenza, Japanese encephalitis, jungle (sylvatic) yellow fever, Junin Argentinian hemorrhagic fever, Kaposi's sarcoma, keratitis, keratoconjunctivitis, Korean Hemorrhagic Fever, kuru, LaCrosse encephalitis, laryngitis, laryngotracheobronchitis (types 1 and 2), Lassa hemorrhagic fever, leukemia, lymphocytic choriomeningitis, lymphoma, Machupo Bolivian hemorrhagic fever, Marburg hemorrhagic fever, Mayaro disease, measles, meningoencephalitis, Molluscum contagiosum, mononucleosis, mononucleosis-like syndrome, multifocal leukoencephalopathy, mumps, nasopharyngeal carcinoma, nausea, neonatal herpes, nephropathia epidemica, ophthalmic herpes zoster, orchitis, orf, parainfluenza, parotitis, pharyngitis, pharyngoconjunctival fever, pleurodynia, pneumonia, polio, poliomyelitis, progressive multifocal leukencephalopathy (PML), rabies, roseola infantum, rubella, rubella panencephalitis, sclerosing panencephalitis, severe acute respiratory syndrome (SARS), shingles (zoster), slapped cheek disease (erythema infectiosum), smallpox, soeola, St. Louis encephalitis, temporal lobe encephalitis, tracheobronchitis, transmissible spongiform encephalopathies, tropical spastic paraparesis, urban yellow fever, urethritis, varicella, verrucae, vomiting, warts, Western equine encephalitis, Yellow fever, zona and/or zoster.

In a preferred embodiment, the compounds of the invention can be used for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms, where the disease and/or pathophysiological condition is selected from the group consisting of "aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, dermatomycosis, dermatophytosis, histoplasmosis, lobomycosis, mucormycosis, mycetoma, mycotic keratitis, oculomycosis, onychomycosis, otomycosis, paracoccidiomycosis, phaeohyphomycosis, piedra, pityriasis versicolor,

- rhinosporidiosis, sporotrichosis, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea favosa, tinea nigra, tinea pedis, tinea unguium, zygomycosis; African trypanosomiasis, American trypanosomiasis, amoebiasis, amoebic dysentery, amoebic keratitis, amoebic meningoencephalitis, amoebic vaginitis, babesiosis, chagas disease,
- 5 coccidiosis, cryptosporidiosis, cutaneous leishmaniasis, cyclosporiasis, dientamoebiasis, entamoebiasis, giardiasis, isosporiasis, lambliasis, leishmaniasis, malaria, malaria quartana, malaria tertiana, malaria tropica, microsporidiosis, mucocutaneous leishmaniasis, pneumocystosis, sarcosporidiosis, sleeping sickness, toxoplasmosis, trichomoniasis, trypanosomiasis, visceral leishmaniasis,
- 10 actinomycosis, acute epiglottitis, acute otitis media, acute purulent (septic) arthritis, acute purulent meningitis, anthrax, appendicitis, bacillary dysentery, bacteremia, black death, borderline leprosy, borreliose, botulism, breast abscesses, bronchitis, brucellosis, bubonic plague, carbuncles, cellulitis, cephalic tetanus, cerebritis, cervicitis, Cholera, conjunctivitis, cutaneous anthrax, cystitis, dermatitis, diarrhea, empyema,
- 15 encephalitis, endocarditis, enteric fever, enteritis, enterocolitis, epididymitis, erysipelas, erysipeloithricosis, exfoliation, extrapulmonary tuberculosis, food poisoning, furuncles, gas gangrene, gastritis, gastroenteritis, gastrointestinal tract (GI) infections, gastrointestinal tuberculosis, genitourinary tuberculosis, glomerulonephritis, hematogenous or lymphohematogenous tuberculosis, impetigo, intra-abdominal
- 20 infections, laryngitis, lepromatous leprosy, leprosy, leptospirosis, listeriosis, Localized tetanus, Lyme disease, mastitis, melioidosis, meningitis, meningoencephalitis, miliary tuberculosis, myonecrosis, nausea, necrotizing enteritis, neonatal listeriosis, neonatal sepsis, nocardiosis, ophthalmitis, osteomyelitis, osteomyelitis, otitis media, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pertussis, Pestis, pharyngitis, plague,
- 25 pneumonia, postpartum sepsis, primary listeremia, proctitis, prostatitis, puerperal sepsis, pulmonary anthrax, pulmonary tuberculosis, Pustular or bullous skin subcutaneous abscesses, pyelonephritis, pyoderma, Rabbit/Deer Fly Fever, rat-bite fever, relapsing fever, rheumatic fever, rhinitis, rhomboencephalitis, salmonellosis, salpingitis, scalded skin syndrome, scarlet fever, sepsis, septic arthritis, septic thrombophlebitis,
- 30 septicemia, shigellosis, sinusitis, skin infections, stitch abscesses, syphilis, tetanus, tick/recurrent/famine fever, tonsillitis, Toxic shock syndrome, tracheobronchitis, treponematoses, tuberculosis, tuberculoid leprosy, tuberculous lymphadenitis, tuberculous meningitis, tuberculous pericarditis, tuberculous peritonitis, tularemia, typhoid fever, ulcer, undulant/Malta/ Mediterranean/Gibraltar Fever, urethritis, urinary
- 35 tract infections (UTIs), vomiting, wound infections, acute febrile respiratory disease

- (AFRD), acute hemorrhagic conjunctivitis, acute hemorrhagic cystitis, acute pharyngoconjunctival fever (APC), acute posterior ganglionitis, acute respiratory disease (ARD), AIDS, arbovirus encephalitis, aseptic meningitis, borna disease, Bornholm disease (pleurodynia), breakbone/dandy fever, bronchiolitis, bronchitis,
- 5 Burkitt's lymphoma, California encephalitis, Castleman's disease, cervical cancer, chickenpox, Chikungunya disease, Colorado tick fever, common cold, conjunctivitis, Cowpox, Creutzfeldt-Jakob disease, Croup, cytomegalic inclusion disease, dengue, dengue hemorrhagic fever, Devil's grip (pleurodynia), Eastern equine encephalitis, Ebola hemorrhagic fever, Ebola virus infection, encephalomyelitis, epidemic
- 10 keratoconjunctivitis (EKC), epidemic nephrosonephritis, erythema infectiosum, fatal familial insomnia, fifth disease, flue, foot and mouth disease (hand-foot-mouth disease), gastroenteritis, geniculate zoster, genital herpes, genital warts, German measles, Gerstmann-Sträussler-Scheinker disease, gingivostomatitis, Hantaan-Korean hemorrhagic fever, hantavirus hemorrhagic fever, hantavirus pulmonary syndrome
- 15 (HPS), hemorrhagic fever with renal syndrome (HFRS), hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, herpangina, herpes labialis, herpes zoster, herpetic stomatitis, HIV infection, Hodgkin's disease, HTLV-I-associated myelopathy, hydrophobia, infectious myocarditis, infectious pericarditis, influenza, Japanese encephalitis, jungle (sylvatic) yellow fever, Junin Argentinian hemorrhagic fever,
- 20 Kaposi's sarcoma, keratitis, keratoconjunctivitis, Korean Hemorrhagic Fever, kuru, LaCrosse encephalitis, laryngitis, laryngotracheobronchitis (types 1 and 2), Lassa hemorrhagic fever, leukemia, lymphocytic choriomeningitis, lymphoma, Machupo Bolivian hemorrhagic fever, Marburg hemorrhagic fever, Mayaro disease, measles, meningoencephalitis, Molluscum contagiosum, mononucleosis, mononucleosis-like
- 25 syndrome, multifocal leukoencephalopathy, mumps, nasopharyngeal carcinoma, nausea, neonatal herpes, nephropathia epidemica, ophthalmic herpes zoster, orchitis, orf, parainfluenza, parotitis, pharyngitis, pharyngoconjunctival fever, pleurodynia, pneumonia, polio, poliomyelitis, progressive multifocal leukoencephalopathy (PML), rabies, roseola infantum, rubella, rubella panencephalitis, sclerosing panencephalitis,
- 30 severe acute respiratory syndrome (SARS), shingles (zoster), slapped cheek disease (erythema infectiosum), smallpox, soeola, St. Louis encephalitis, temporal lobe encephalitis, tracheobronchitis, transmissible spongiform encephalopathies, tropical spastic paraparesis, urban yellow fever, urethritis, varicella, verrucae, vomiting, warts, Western equine encephalitis, Yellow fever, zona and/or zoster as well as their different
- 35 forms and subforms" and preferably is selected from the group consisting of

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“trypanosomiasis, American trypanosomiasis, chagas disease, leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis, malaria, malaria tropica, toxoplasmosis, acute otitis media, bronchitis, dermatitis, encephalitis, endocarditis, gastritis, gastroenteritis, gastrointestinal tract (GI) infections, laryngitis, meningitis, otitis media, pericarditis, pharyngitis, pneumonia, sepsis, sinusitis, skin infections, tuberculosis and/or urinary tract infections (UTIs) as well as their different forms and subforms”.

In another aspect, the object of the invention has surprisingly been solved by providing the compounds of the invention for use for the manufacture of a medicament for the treatment of tumors in mammals.

The term “tumor” or “cancer” is intended for the purpose of the present invention to comprise all known mammalian benign and/or malign tumors, i.e. the various known tumors, cancers, neoplasms and/or ulcers of any tissue and/or organ in mammals, such as the ones illustrated for instance in “Encyclopedic Reference of Cancer, Ed: Manfred Schwab, Springer-Verlag Berlin Heidelberg 2001 (ISBN 3-540-66527-7)”.

As illustrated supra, the compounds of the invention are useful for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals as defined herein. They can be administered to various mammalian species, including human.

For the purpose of the present invention, all mammalian species are regarded as being comprised. In a preferred embodiment, such mammals are selected from the group consisting of “human, domestic animals, cattle, livestock, pets, cow, sheep, pig, goat, horse, pony, donkey, hinny, mule, hare, rabbit, cat, dog, guinea pig, hamster, rat, mouse”. More preferably, such mammals are humans.

In a further aspect of the present invention, the compounds of the invention are used in combination with at least one additional pharmacologically active substance.

Depending on the purpose of the combined use, such additional pharmacologically active substance may be other alkyl phospholipid derivatives (the compounds of the invention and/or known alkyl phospholipid derivatives, such as miltefosine, perifosine and/or erucylphosphocholine) and/or other “suitable therapeutic agents” useful in the

treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions. Selection and combination of the additional pharmacologically active substance(s) can be easily performed by the skilled artisan on the basis of his expert knowledge and depending on the purpose of the combined use and diseases and/or pathophysiological conditions targeted.

The above mentioned "suitable therapeutic agents" include benznidazole (N-Benzyl-2-nitroimidazol-1-yl-acetamide; CAS Registry Number: 22994-85-0); nifurtimox [3-Methyl-4-(5-nitrofurfuryl-idenamino)tetrahydro-1,4-thiazine-1,1-dioxide; CAS Registry Number: 23256-30-6]; amphotericin B [(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-mannopyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19, 21, 23, 25, 27, 29, 31-heptaene-36-carboxylic acid; CAS Registry Number: 1397-89-3]; liposomal amphotericin B (AmBisome™; Gilead Sciences, Inc., Astellas Pharma US, Inc.), sitamaquine (N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinoliny)-1,6-Hexanediamine; CAS Registry Number: 57695-04-2) and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine; CAS Registry Number: 7542-37-2] and preferably, a "suitable therapeutic agents" is selected of the group consisting of these agents.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

25

In a preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions in the form of a medicament, where such medicament comprises at least one additional pharmacologically active substance.

30

In another preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions in the form of a medicament, where the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance.

In a preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions in the form of a medicament, where such medicament comprises at least one compound of the invention and at least one additional pharmacologically active substance selected from the group consisting of "benznidazole (N-Benzyl-2-nitroimidazol-1-yl-acetamide); nifurtimox [3-Methyl-4-(5-nitrofurfuryl-idenamino)tetrahydro-1,4-thiazine-1,1-dioxide]; amphotericin B [(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-mannopyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid]; liposomal amphotericin B, sitamaquine (N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinoliny)-1,6-Hexanediamine; CAS Registry Number: 57695-04-2) and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine]".

More preferably such diseases and/or pathophysiological conditions are selected from the group consisting of "trypanosomiasis, American trypanosomiasis, chagas disease, leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis, malaria and/or malaria tropica as well as their different forms and subforms".

In another preferred embodiment, the compounds of the invention are used for the treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions in the form of a medicament, where the medicament comprising at least one compound of the invention is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance selected from the group consisting of "benznidazole (N-Benzyl-2-nitroimidazol-1-yl-acetamide); nifurtimox [3-Methyl-4-(5-nitrofurfuryl-idenamino)tetrahydro-1,4-thiazine-1,1-dioxide]; amphotericin B [(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-mannopyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid]; liposomal amphotericin B, sitamaquine (N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinoliny)-1,6-

Hexanediamine; CAS Registry Number: 57695-04-2) and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine]".

5 More preferably such diseases and/or pathophysiological conditions are selected from the group consisting of "trypanosomiasis, American trypanosomiasis, chagas disease, leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis, malaria and/or malaria tropica as well as their different forms and subforms".

10 In yet a further aspect, the object of the invention has surprisingly been solved by using alkyl phospholipid derivatives selected from the group consisting of "miltefosine (hexadecylphosphocholine), perifosine (octadecyl-1,1-dimethyl-piperidino-4-yl-phosphate) and/or erucylphosphocholine [(13Z)-docosenylphosphocholine]" in the form of a medicament for the treatment or prophylaxis of the aforementioned diseases
 15 and/or pathophysiological conditions in mammals that are caused by microorganisms as variously illustrated herein, where such medicament comprises at least one additional pharmacologically active substance selected from the group consisting of "benznidazole (N-Benzyl-2-nitroimidazol-1-yl-acetamide); nifurtimox [3-Methyl-4-(5-nitrofurfuryl-idenamino)tetrahydro-1,4-thiazine-1,1-dioxide]; amphotericin B [(1R, 3S, 20 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-manno-pyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid]; liposomal amphotericin B, sitamaquine (N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinoliny)-1,6-Hexanediamine;
 25 CAS Registry Number: 57695-04-2) and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine]" and an alkyl phospholipid derivative selected from the group consisting of "miltefosine (hexadecylphosphocholine), perifosine (octadecyl-1,1-dimethyl-piperidino-4-yl-phosphate) and/or
 30 erucylphosphocholine [(13Z)-docosenyl-phosphocholine]".

In yet a further aspect, the object of the invention has surprisingly been solved by using alkyl phospholipid derivatives selected from the group consisting of "miltefosine (hexadecylphosphocholine), perifosine (octadecyl-1,1-dimethyl-piperidino-4-yl-phosphate) and/or erucylphosphocholine [(13Z)-docosenyl-phosphocholine]" in the

form of a medicament for the treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions in mammals that are caused by microorganisms as variously illustrated herein, where the medicament is applied before and/or during and/or after treatment with at least one additional pharmacologically active substance selected from the group consisting of "benznidazole (N-Benzyl-2-nitroimidazol-1-yl-acetamide); nifurtimox [3-Methyl-4-(5-nitrofurfuryl-idenamino)tetrahydro-1,4-thiazine-1,1-dioxide]; amphotericin B [(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-manno-pyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1] nonatriaconta-19,21,23,25,27,29,31-heptaene-36-carboxylic acid]; liposomal amphotericin B, sitamaquine (N,N-diethyl-N'-(6-methoxy-4-methyl-8-quinoliny)-1,6-Hexanediamine; CAS Registry Number: 57695-04-2) and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine]".

More preferably such diseases and/or pathophysiological conditions are selected from the group consisting of "trypanosomiasis, American trypanosomiasis, chagas disease, leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis, malaria and/or malaria tropica as well as their different forms and subforms".

Even more preferably, such medicament comprises miltefosine and amphotericin B, liposomal amphotericin B, sitamaquine and/or paromomycin and is used for the treatment of leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis and/or visceral leishmaniasis as well as their different forms and subforms.

Even more preferably, such medicament comprises miltefosine and benznidazole and/or nifurtimox and is used for the treatment of trypanosomiasis, American trypanosomiasis and/or chagas disease as well as their different forms and subforms.

Most preferably, such medicament comprises miltefosine and benznidazole and is used for the treatment of trypanosomiasis, American trypanosomiasis and/or chagas disease, in particular chronic forms of trypanosomiasis, American trypanosomiasis and/or chagas disease, that are caused by *Trypanosoma cruzi* epimastigote forms and/or especially *Trypanosoma cruzi* amastigote forms. *Trypanosoma cruzi* amastigotes represent the intracellular form of the *Trypanosoma cruzi* parasites that are mainly responsible for the chronic course of disease. *Trypanosoma cruzi*

amastigotes form nests in the myocardle muscle, which leads to cardiac insufficiency and ultimately cardiomyopathy. Treatment or prophylaxis against *Trypanosoma cruzi* epimastigote and/or in particular *Trypanosoma cruzi* amastigotes, in particular cardiac insufficiency and/or cardiomyopathy caused by these parasite forms, is therefore
5 preferred.

In a preferred embodiment, the compounds of the invention or alkyl phospholipid derivatives selected from the group consisting of "miltefosine (hexadecylphosphocholine), perifosine (octadecyl-1,1-dimethyl-piperidino-4-yl-
10 phosphate) and/or erucylphosphocholine [(13Z)-docosenyl-phosphocholine]" are used for the treatment and/or prophylaxis of the aforementioned diseases and/or pathophysiological conditions in the form of a pharmaceutical kit, where such pharmaceutical kit comprises at least one additional pharmacologically active substance as described herein.

15

The compounds of the invention are surprisingly characterized by their improved action and/or improved efficacy against the various bacteria, fungi, protozoa and/or viruses as well as in the treatment of respective diseases and/or pathophysiological conditions thereof. Due to their surprisingly strong action and/or efficacy, the
20 compounds of the invention may be advantageously administered at lower doses compared to other known but less potent APL or other relevant therapeutic agents while still achieving equivalent or even superior desired biological effects. In addition, such a dose reduction may translate into less or even no medicinal adverse effects.

Furthermore, the compounds of the invention are surprisingly less cytotoxic than
25 known APL or other relevant therapeutic agents while being of at least equivalent if not superior potency. Therefore, use of the compounds of the invention in the treatment of the herein mentioned diseases and/or pathophysiological conditions – even at unreduced doses – may lead to less or even no medicinal adverse effects.

Besides, the compounds of the invention are surprisingly less embryotoxic or even
30 not embryotoxic at all compared to known APL or other relevant therapeutic agents while being of at least equivalent if not superior potency. Embryotoxicity is the ability of a substance to cause harm/be toxic to the embryo, resulting in abnormal development or death.

Moreover, combined use of the compounds of the invention, but also miltefosine, perifosine and/or erucylphosphocholine, with known standard therapeutic agents (e.g. benznidazole, nifurtimox, amphotericin B, liposomal amphotericin B and/or
5 paromomycin) in the treatment of herein mentioned diseases and/or pathophysiological conditions is surprisingly characterized by a superior efficacy compared to the (standard) treatment with the single therapeutic agents alone.

Besides, such combination treatment surprisingly allows a dose reduction of the additional therapeutic agents (e.g. benznidazole, nifurtimox, amphotericin B, liposomal
10 amphotericin B and/or paromomycin) applied compared to their single use while being of at least equivalent if not superior efficacy. In addition, such a dose reduction may translate into less or even no medicinal adverse effects.

Furthermore, such combination treatment surprisingly allows a significant time reduction, i.e. shorter courses of treatment, which is advantageous in view of patient
15 compliance and economic healthcare aspects.

The alkyl phospholipid derivative compounds disclosed herein and/or where appropriate additional pharmacologically active substances can be administered in a known manner. The route of administration may thereby be any route which effectively
20 transports the active compound to the appropriate or desired site of action, for example orally or non-orally, in particular topically, transdermally, pulmonary, rectally, intravaginally, nasally or parenteral or by implantation. Oral administration is preferred.

The alkyl phospholipid derivative compounds disclosed herein and/or where
25 appropriate additional pharmacologically active substances are converted into a form which can be administered and are mixed where appropriate with pharmaceutically acceptable carriers or diluents. Suitable excipients and carriers are described for example in Zanowski P, Ullmann's Encyclopedia of Industrial Chemistry 2005, Pharmaceutical Dosage Forms, 1-33; Spiegel AJ et al., Journal of Pharmaceutical
30 Sciences 1963, 52: 917-927; Czetsch-Lindenwald H, Pharm. Ind. 1961, 2: 72-74; Fiedler HP, Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete 2002, Editio Cantor Verlag, p65-68.

Oral administration can take place for example in solid form as tablet, capsule, gel capsule, coated tablet, granulation or powder, but also in the form of a drinkable solution. The alkyl phospholipid derivative compounds disclosed herein can for oral administration be combined with known and ordinarily used, physiologically tolerated excipients and carriers such as, for example, gum arabic, talc, starch, sugars such as, for example, mannitol, methylcellulose, lactose, gelatin, surface-active agents, magnesium stearate, cyclodextrins, aqueous or nonaqueous carriers, diluents, dispersants, emulsifiers, lubricants, preservatives and flavorings (e.g. essential oils). The alkyl phospholipid derivative compounds disclosed herein can also be dispersed in a microparticulate, e.g. nanoparticulate, composition.

Non-oral administration can take place for example by intravenous, subcutaneous, intramuscular injection of sterile aqueous or oily solutions, suspensions or emulsions, by means of implants or by ointments, creams or suppositories. Administration as sustained release form is also possible where appropriate. Implants may comprise inert materials, e.g. biodegradable polymers or synthetic silicones such as, for example, silicone rubber. Intravaginal administration is possible for example by means of vaginal rings. Intrauterine administration is possible for example by means of diaphragms or other suitable intrauterine devices. Transdermal administration is additionally provided, in particular by means of a formulation suitable for this purpose and/or suitable means such as, for example, patches.

The dosage may vary within a wide range depending on type and/or severity of the disease and/or pathophysiological condition, the mode of administration, the age, gender, bodyweight and sensitivity of the subject to be treated. It is within the ability of a skilled worker to determine a "pharmacologically effective amount" of an alkyl phospholipid derivative compound as disclosed herein and/or additional pharmacologically active substance. Administration can take place in a single dose or a plurality of separate dosages.

A suitable unit dose is, for example, from 0.001 mg to 100 mg of the active ingredient, i.e. at least one alkyl phospholipid derivative compounds as disclosed herein and, where appropriate, at least one additional pharmacologically active substance, per kg of a patient's bodyweight.

Chemical synthesis

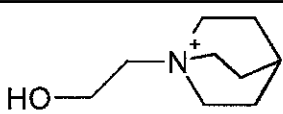
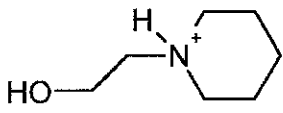
Synthesis of alkyl phospholipid derivative compounds as disclosed herein is a procedure well described in the prior art and known to the skilled artisan due to his expert knowledge. In this context reference is expressly made to the following patent literature as well as the literature cited therein: EP 0 108 565 A2; WO 87/03478; US 5,980,915; US 6,254,879; US 6,506,393; US 6,172,050; US 6,479,472; US 5,449,798; US 5,958,906.

In the following, further details of syntheses of specific head and tail groups are given. For the avoidance of doubt, it is explicitly stated that the different R residues named in the chemical synthesis section do not correspond to those defined above for formula (I) and specific subsets. Hence, they may differ or have the same meaning.

A)

Some nitrogen containing head groups were synthesized by alkylation of an amine (see table 1 and general procedure 1).

Table 1

Compound	Nitrogen Containing Head Group
3	
19	

General procedure 1:

where R1 represents a choline derivative and R2 represent the herein disclosed substituted and/or unsubstituted alkyl radicals.

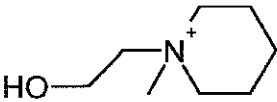
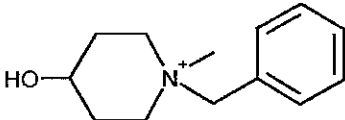
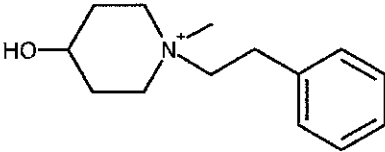
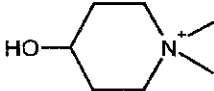
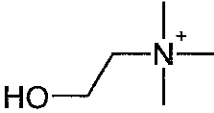
0.3 mol amine, 150 ml CH₃CN and catalytical amounts of KI are placed in a reaction vessel. The alkoxy bromide is dropped to this mixture at room temperature, stirred for 15 min and then heated to reflux for 2d. After concentration in vacuo, the
 5 residue is crystallized from acetone. Yields vary from 10 to 50%.

When appropriate, other amine alkylating agents (e.g. benzyl bromide or phenetyl bromide) may also be used.

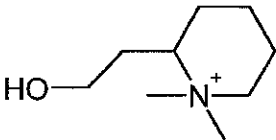
10 B)

Other nitrogen containing head groups were synthesized by methylation (see table 2 and general procedure 2).

Table 2

Compound	Methylated Nitrogen Containing Head Group
2, 20	
1	
4	
6, 7, 10, 12, 13, 15, 17	
8, 11, 14, 16	

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9	
---	--

General procedure 2:

where R3 represents a choline derivative and R4 represent the herein disclosed
 5 substituted and/or unsubstituted alkyl radicals.

0,5 mol of the choline derivative and 125 ml CH₃CN are placed in a reaction vessel.
 0,5 mol p-toluene sulfonic acid methyl ester in 125 ml CH₃CN are added dropwise
 while keeping reaction temperatures below 10°C. After stirring for 30 min at room
 10 temperatur, the mixture is heated to reflux for another 30 min and cooled to room
 temperatur. The resulting solid ("tosylate") is isolated (if applicable under inert
 atmosphere), crystallized from 125 ml isopropanol and dried over P₂O₅ in vacuo.
 Yields vary from 40 to 60%.

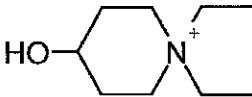
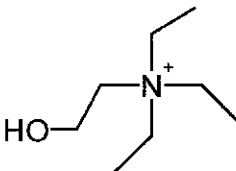
15 Alternatively, methyl halogenids may also be used for methylation.

C)

Other nitrogen containing head groups were synthesized by ethylation (see table 3
 and general procedure 3).

20

Table 3

Compound	Nitrogen Containing Head Group
5	
18	

General procedure 3:

where R5 represents a choline derivative and R6 represents the herein disclosed substituted and/or unsubstituted alkyl radicals.

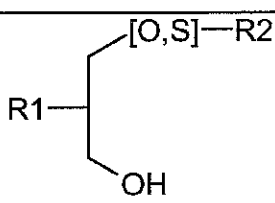
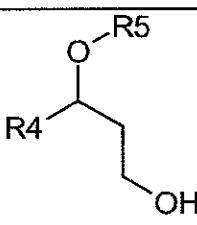
- 5 0,5 mol of the choline derivative and 125 ml CH₃CN are placed in a reaction vessel. 0,5 mol ethyl bromide in 125 ml CH₃CN are added dropwise while keeping reaction temperatures below 10°C. After stirring for 30 min at room temperatur, the mixture is heated to reflux for another 30 min and cooled to room temperatur. The resulting solid ("bromide") is isolated (if applicable under inert atmosphere), recrystallized from 125 ml isopropanol and dried over P₂O₅ in vacuo. Yields vary from 40 to 60%.

Alternatively, ethyl iodine may also be used.

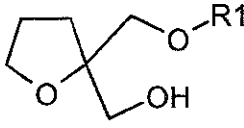
D)

- 15 The various lipophilic tail groups, which are attached to the phosphate moiety, may be used as exemplified in the following ways (see table 4).

Table 4

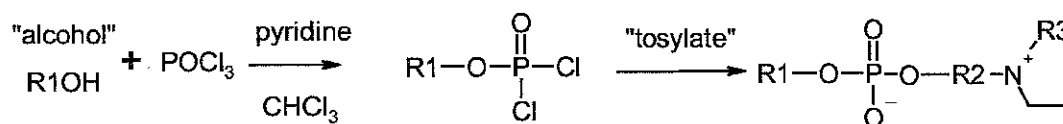
Compound	Lipophilic Tail Group
1, 2, 3, 4, 5, 9, 16, 17, 18, 19	Saturated alkyl chains: C16, C18 Unsaturated alkylchains: C20, C22
6, 12, 13, 15	 were R1 is alkoxy or alkylalkoxy and R2 is C16, C18
14	 were R4 is alkylsulfonyl alkyl ester and R5 is C16

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7, 10, 11	 were R1 is C16, C18
8, 20	Alkoxy-alkoxy chains

E)

Alkyl phospholipid derivative compounds 1-20 were synthesized according to the below mentioned general procedure 4, where "tosylate" denotes the nitrogen containing head group and "alcohol" denotes the lipophilic tail group.

General procedure 4:

10

In a reaction vessel, 0.1 mol POCl₃ are placed in 50 ml Chloroform and cooled in an ice bath. A solution of 0.9 mol "alcohol" and 32 ml pyridine in 100ml CH₂Cl₂ is dropped to the POCl₃ solution while keeping the temperature between 5-12° C. After stirring for 30min at room temperature, 0.12 mol "tosylate" are added, cooled to 10° C and 40 ml pyridine is dropped to this solution. The mixture is stirred for 2.5 h at room temperature. 15 ml water are added (T < 20° C) and stirring is continued for another 30 min. The mixture is washed with 200 ml H₂O : MeOH (1:1 v/v), 200 ml 3% HCl : MeOH (1:1 v/v) and 200 ml H₂O : MeOH (1:1 v/v). The organic phase is concentrated in vacuo (isopropanol is added in order to diminish foaming). The crude product is recrystallized from 200 ml methyl ethyl ketone. The resulting solid is heated in 150 ml EtOH, filtrated, cooled for 4 h to 5-7° C and again filtrated. 85 g Amberlite MB3 are added to the filtrate and stirred for 3 h at room temperature. After filtrating, the clear solution is concentrated in vacuo and recrystallized from 150ml methyl ethyl ketone. If applicable, the product is purified by column chromatography (CH₂Cl₂ / MeOH / NH₃ (25%) 80 : 25 : 5). Yields vary from 25 to 50%.

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The contents of all cited references and patents are hereby incorporated by reference in their entirety.

The invention is explained in more detail by means of the following examples without, however, being restricted thereto.

Examples**I) Synthesis / physicochemical characterization of selected alkyl phospholipid derivate compounds**

5

Example 1: Compound 1

Phosphoric acid 1-benzyl-1-methyl-piperidin-4-yl ester hexadecyl ester

3.1g (6%) of compound 1 was obtained starting from hexadecan-1-ol and 1-benzyl-piperidine-4-ol according to general procedure 4 after methylating 1-benzyl-piperidine-4-ol according to general procedure 2.

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 7.59 (2H, d), 7.47-7.40 (3H, m), 4.78 (2H, broad-s), 4.55 (1H, broad-s), 3.86-3.77 (4H, m), 3.56 (2H, d), 3.13 (3H, s), 2.27 (2H, d), 2.13 (2H, t), 1.57 (2H, quintet), 1.31-1.18 (26H, m), 0.88 (3H, t) ppm

ESI-MS: found: m/z 510.4 [M+H], calculated: 510.7 g/mol

Example 2: Compound 2

Phosphoric acid hexadecyl ester 2-(1-methyl-piperidin-1-yl)-ethyl ester

5.8g (13%) of compound 2 was obtained starting from hexadecan-1-ol and 2-piperidine-1-yl-ethanol according to general procedure 4 after methylating 2-piperidine-1-yl-ethanol according to general procedure 2.

25

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 4.33 (2H, broad-s), 3.89-3.81 (4H, m), 3.70 (2H, m), 3.57-3.53 (2H, m), 3.37 (3H, s), 1.93-1.86 (4H, m), 1.74-1.68 (2H, m), 1.59 (2H, quintet), 1.35-1.19 (26H, m), 0.88 (3H, s) ppm

ESI-MS: found: m/z 448.3 [M+H], calculated: 448.6 g/mol

30

Example 3: Compound 3

Phosphoric acid 2-(1-aza-bicyclo[2.2.2]oct-1-yl)-ethyl ester hexadecyl ester

- 5 2,0g (5%) of compound 3 was obtained starting from starting from hexadecan-1-ol and 1-(2-hydroxy-ethyl)-chinuclidine according to general procedure 4 after alkylating chinuclidine according to general procedure 1.

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 4.29 (2H, broad-s), 3.84 (2H, q), 3.73 (8H, m),
10 2.17 (1H, m), 1.60 (2H, quintet), 1.34-1.22 (26H, m), 0.88 (3H, t) ppm

ESI-MS: found: m/z 460.5 [M+H], calculated: 460.7 g/mol

Example 4: Compound 4

- 15 Phosphoric acid hexadecyl ester 1-methyl-1-phenethyl-piperidin-4-yl ester

6.3g (12%) of compound 4 was obtained starting from hexadecan-1-ol and 1-phenethyl-piperidine-4-ol according to general procedure 4 after methylating 1-phenethyl-piperidine-4-ol according to general procedure 2.

20

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 7.34-7.22 (5H, m), 4.49 (1H, broad-s), 3.80 (2H, q), 3.77-3.58 (6H, m), 3.29 (3H, s), 3.10 (2H, dd), 2.24 (2H, m), 2.10 (2H, m), 1.59 (2H, quintet), 1.31-1.19 (26H, m), 0.88 (3H, t) ppm

- 25 ESI-MS: found: m/z 524.4 [M+H], calculated: 524.8 g/mol

Example 5: Compound 5

Phosphoric acid 1,1-diethyl-piperidin-4-yl ester octadecyl ester

- 30 6.9g (14%) of compound 5 was obtained starting from octadecan-1-ol and 1-ethyl-

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piperidin-4-ol according to general procedure 4 after alkylating 1-ethyl-piperidin-4-ol according to general procedure 3.

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 4.50 (1H, broad-s), 3.81 (2H, q), 3.71 (2H, m),
5 3.62 (2H, m), 3.51 (2H, q), 3.46 (2H, q), 2.25-2.09 (4H, m), 1.58 (2H, quintet), 1.38-
1.21 (36H, m), 0.88 (3H, t) ppm

ESI-MS: found: m/z 490.6 [M+H]⁺ / calculated: 490.8 g/mol

10 Example 6: Compound 8

Phosphoric acid 3-hexadecyloxy-propyl ester 2-trimethyl-ammonium-ethyl ester

9.3g (20%) of compound 8 was obtained starting from 3-hexadecyloxy-propan-1-ol and
2-dimethylamino-ethanol according to general procedure 4 after methylating 2-
15 dimethylamino-ethanol according to general procedure 2.

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 4.32 (2H, broad-s), 3.93 (2H, q), 3.83 (2H,
bs), 3.50 (2H, t), 3.42 (9H, s), 3.39 (2H, t), 1.89 (2H, quintet), 1.54 (2H, quintet), 1.34-
1.22 (26H, m), 0.88 (3H, t) ppm

20

ESI-MS: found: m/z 466.5 [M+H]⁺, calculated: 466.7 g/mol

Example 7: Compound 22

Phosphoric acid octadecyl ester 2-(N,N,N-trimethyl-arsen)-ethyl ester

25

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 4.28 (2H, q), 3.85 (2H, q), 2.94 (2H, t), 2.14
(9H, s), 1.62 (2H, quintet), 1.37-1.21 (30H, m), 0.90 (3H, s) ppm

ESI-MS: found: m/z 497.3 [M+H]⁺, calculated: 496.5 g/mol

30

Example 8: Compound 89

Phosphoric acid hexadecyl ester 2-(1-methyl-azepan-1-yl)-ethyl ester

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 4.66 (2H, m), 4.06 (2H, q), 4.02 (2H, broad-s),
5 3.80 (2H, dd), 3.59 (2H, dd), 3.36 (3H, s), 2.02-1.90 (4H, m), 1.74 (4H, m), 1.67 (2H,
quintet), 1.37-1.22 (26H, m), 0.88 (3H, s) ppm

ESI-MS: found: m/z 462.5 [M+H], calculated: 461.6 g/mol

10 Example 9: Compound 107

Phosphoric acid hexadecyl ester 2-(N-phenyl-N,N-dimethyl-amino)-ethyl ester

¹H-NMR (600MHz, CDCl₃-d₁, 300K): δ = 7.99 (2H, d), 7.65 (2H, t), 7.55 (1H, t), 4.90
(2H, broad-s), 4.24 (2H, broad-s), 4.02-4.00 (6H, m), 3.93 (2H, q), 1.57 (2H, quintet),
15 1.32-1.22 (26H, m), 0.88 (3H, s) ppm

ESI-MS: found: m/z 470.5 [M+H], calculated: 469.64 g/mol

Physicochemical data on further exemplified alkyl phospholipid derivative compounds
20 are compiled in **Table 5** below:

Table 5: Exemplified alkyl phospholipid derivative compounds with synthesis schemes and MS data:

No.	Synthesis schemes	[M+H] (calculated)	ESI-MS found (M+H)⁺
6	2,4	552.8	542.4
7	2,4	548.8	548.5
9	2,4	476.7	476.5
10	2,4	576.8	576.4
11	2,4	522.7	522.5
12	2,4	522.7	522.7
13	2,4	536.7	536.5
14	2,4	558.8	558.4
15	2,4	550.8	550.5
16	2,4	462.7	462.4
17	2,4	516.8	516.5
18	3,4	422.6	422.3
19	4	460.7	460.5
20	2,4	452.6	452.4
22		496.5	497.4
27		538.8	538.8
30		408.6	408.4
33		436.6	436.4
35		448.6	448.4
40		464.7	464.3
41		554.9	554.6
42		406.6	406.2
43		434.6	434.4
47		492.8	492.5
49		462.9	462.3
51		450.7	450.4
55		432.6	432.3
56		450.7	450.4
57		394.5	394.6
60		436.6	436.3
66		450.6	450.4
67		445.6	445.3
68		594.4	594.2
70		436.6	436.4
75		434.6	434.5
76		446.6	446.3
80		490.7	490.5
81		466.7	466.5

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93		490.7	490.6
95		459.6	459.5
98		462.7	462.3
99		492.7	492.3
103		474.7	474.5
106		490.7	490.6
107		470.6	470.4
108		464.7	464.3
109		488.7	488.4
112		448.6	448.3
113		476.5	476.5
115		504.7	504.4
116		462.7	462.4
117		460.7	460.4
124		476.7	476.4
133		546.8	546.4
134		532.8	532.5
136		450.7	450.4
138		448.7	448.3
139		504.8	504.5
146		476.7	476.5
154		491.7	491.5
155		478.3	478.3
169		460.7	460.5
171		494.7	494.3
176		488.7	488.5
179		564.8	564.3
192		536.7	536.5
195		538.8	538.5
197		538.8	538.5
204		550.1	550.5
211		564.8	564.6
213		550.8	550.4
215		504.7	504.5
233		614.9	614.4
236		849.1	849.4
243		594.9	594.4
257		875.1	875.5
275		532.8	532.5
296		488.7	488.4
298		576.8	576.3
305		496.7	496.4
309		578.8	578.5
314		436.8	436.5

II) Assay for assessing cytotoxicity against mammalian cell lines

Cytotoxicity of selected compounds of the invention against different mammalian cell lines was assessed as follows.

Human tumor cell lines KB/HeLa (ATCC CCL17, human cervix carcinoma), PC3
5 (ATCC CRL1435, human prostate carcinoma) and RKOp21 (human colon
adenocarcinoma; Schmidt et al., Oncogene 2000, 19: 2423-2429) cells were used in an
automated XTT screening assay for the assessment of cytotoxicity.

Further mammalian cell lines that can be tested in the automated XTT screening
assay for the assessment of cytotoxicity are FDCP-1 (DSMZ ACC 368, mouse bone
10 marrow), H9c2 (2-1) (ECACC 88092904, rat heart), L8 (ECACC 95102434, rat skeletal
muscle), C2C12 (ECACC 91031101, mouse skeletal muscle), CHO (ECACC
85050302, Chinese Hamster ovary), NRK-52E (ECACC 87012902, rat kidney), NRK-
49F (ECACC 86101301, rat kidney), MDCK (ECACC 84121903/ATCC CCL-34, canine
cocker spaniel kidney), HepG2 (ATCC HB-8065, human hepatocellular carcinoma),
15 NIH3T3 (ATCC CRL-1658, mouse fibroblast), HaCaT (Deutsches
Krebsforschungszentrum (DKFZ), human keratinocyte) as well as primary cells, such
as primary rat hepatocytes.

The XTT assay quantifies cellular metabolic activity which correlates with cell
20 viability and cell number. Test compounds (selected compounds of the invention and
known substances as controls) are dissolved in culture medium at 600 μ M and added to
the tumor cells in 10 different concentrations in a semi-logarithmic fashion starting from
100 μ M as highest concentration.

In a second set of experiments employing PC3, RKOp21 and SKOV-3 (ATCC HTB-
25 77, human ovary adenocarcinoma) cells, test and reference compounds were
dissolved in 70% Ethanol/30% H₂O in a stock concentration of 10 mM and diluted in
cell culture medium to yield either 31.6 μ M (PC3 and RKOp21) or 100 μ M (SKOV-3)
final concentration.

48h later cellular metabolic activity of cells treated with test compounds is quantified
30 by measurement of the absorbance at 490nm (conversion of XTT dye) in comparison
to untreated control cells (100% viability).

KB/HeLa and PC3 cells were cultivated in RPMI 1640 medium (Gibco, Cat.No.
42401-018) supplemented with 10% heat inactivated fetal calf serum (FCS, Biochrom

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AG, Cat.No. S0115), 2 mM L-glutamine (Gibco, Cat.No. 25030-24) and 2% Penicillin-Streptomycin (PenStrep, Gibco, Cat.No. 15140-122). RKOp21 cells were grown in DMEM + GlutaMAXTM-I medium (Gibco, Cat.No. 61965-026) supplemented with 10% heat inactivated fetal calf serum (FCS, Biochrom AG, Cat.No. S0115), 2 mM L-glutamine (Gibco, Cat.No. 25030-24), 2% Penicillin-Streptomycin (PenStrep, Gibco, Cat.No. 15140-122) and 1% 1M HEPES (Gibco, Cat.No. 15630-056). All cells were cultured at 37°C in 5% CO₂ humidified air.

On the first day of the experiment cells were harvested from exponential phase cultures by trypsination, counted and plated into 96 well flat-bottom micro titer plates depending on the cell line as listed below:

Cell Line	Number / Well	Volume / Well
KB/HeLa	2500	125 µl
PC3	6000	125 µl
RKOp21	6000	125 µl
SKOV3	3750	125 µl

After a 24h recovery to allow the cells to resume exponential growth, the test compounds were diluted immediately prior to use and transferred in 25µl volume to the wells.

Following 2 days of continuous drug exposure 50µl of freshly prepared XTT-PMS solution {2% 0.386mg/ml PMS (N-Methyl Dibenzipyrazine Methylsulphate; Sigma, Cat.No. P9625) in PBS + 98% 1mg/ml XTT (Sodium 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5-[(phenylamino)carbonyl]-2H-Tetrazolium; Serva, Cat.No. 38450) in RPMI 1640 medium without phenol red} was added to the wells. To measure the proportion of living cells, the cells were incubated for 3 h with XTT-PMS reagent at 37°C, 5% CO₂, humidified atmosphere allowing to form the formazan salt. The amount of soluble formazan salt produced by cellular reduction of XTT is quantified by measuring the absorbance at 490nm using the Biomek[®] 2000 ELISA plate reader.

%-inhibition (cytotoxicity) of each test compound was calculated in relation to untreated control cells. Inhibition curves were generated and IC₅₀ values calculated by using GraphPad Prism.

In the following **table 6** cytotoxicity results (IC_{50} values) obtained for selected compounds of the invention are presented in comparison to examples of the prior art (perifosine, miltefosine).

5

Table 6: Cytotoxicity assay results for mammalian RKOp21, KB/HELA and PC3 cell lines (IC_{50} values for a number of selected exemplary compounds)

Compound	RKOp21 [IC_{50} (μ M)]	PC3 [IC_{50} (μ M)]	KB/HELA [IC_{50} (μ M)]
17	32,47	18,28	16,59
19	>100	>100	>100
20	>100	>100	>100
25	>100	12,78	23,91
41	>100	>100	>100
46	>100	>100	>100
48	>100	>100	>100
50	>100	>100	>100
55	>100	>100	>100
59	>100	>100	>100
60	>100	>100	>100
63	>100	>100	>100
67	>100	>100	>100
72	>100	>100	>100
76	68,80	24,99	11,27
82	20,53	45,61	37,73
85	>100	32,90	43,66
86	>100	>100	75,64
91	>100	86,79	>100
97	89,37	49,44	>100

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114	>100	>100	>100
116	39,97	50,25	37,72
123	76,62	21,83	39,08
128	>100	26,13	13,78
133	>100	81,58	>100
144	51,14	>100	>100
145	>100	>100	>100
147	>100	>100	>100
152	>100	23,90	32,32
153	>100	39,82	38,25
154	77,43	18,25	12,62
159	21,01	37,70	>100
172	65,52	29,82	>100
173	>100	64,47	>100
176	67,04	13,41	16,87
180	>100	>100	>100
185	>100	30,36	>100
190	>100	73,27	100,00
200	>100	34,52	66,38
203	>100	63,12	>100
235	>100	>100	>100
237	46,84	>100	>100
240	>100	>100	>100
256	>100	82,00	>100
257	25,06	29,68	19,22
258	>100	>100	>100
262	>100	31,25	10,10
263	>100	>100	>100

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275	44,44	69,15	>100
281	95,20	16,57	20,64
282	>100	>100	>100
301	34,43	24,38	20,41
302	>100	>100	>100
306	53,45	18,65	34,31
311	>100	>100	>100
miltefosine	18,04	9,39	8,66
perifosine	3,31	3,22	2,37

The result presented in **table 6** clearly demonstrate the favorable lower cytotoxicity of the selected compounds of the invention compared to prior art compounds perifosine and miltefosine.

5

In the following **table 7** cytotoxicity results (% inhibition of cell growth) obtained in the second set of experiments for selected compounds of the invention are presented in comparison to examples of the prior art (perifosine, miltefosine). The results presented are individual values for the respective cell line as well as the mean value

10

over all three cell lines tested.

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Table 7: Cytotoxicity assay results for mammalian PC3, RKOp21 and SKOV-3 cell lines (% Inhibition, %INH)

Compound	PC3 %INH [31,6 μ M]	RKOp21 %INH [31,6 μ M]	SKOV-3 %INH [100 μ M]	Mean %INH
2	50,1	38,8	19,5	36,1
19	16,2	53,4	26,9	32,2
20	13,4	-12,4	-6,1	-1,7
89	50,6	11,3	26,1	29,3
90	55,5	51,9	54,6	54,0
144	14,0	48,0	-3,0	19,7
260	45,2	40,5	56,1	47,3
266	25,8	6,6	8,5	13,6
307	48,4	18,3	53,3	40,0
314	51,6	10,6	33,2	31,8
miltefosine	67,4	64,0	74,7	68,7
perifosine	80,2	63,0	90,7	78,0

- 5 The result presented in **table 7** clearly demonstrate the favorable lower cytotoxicity of the selected compounds of the invention over all three cell lines tested compared to prior art compounds perifosine and miltefosine.

III) Assay for assessing embryotoxicity against mammalian cell lines

Interaction of chemicals with the differentiation process during foetal development can cause embryotoxicity. The model of *in vitro* embryonic stem cell test (EST) has the potential to screen chemical compounds *in vitro* for their ability to interact and disturb this differentiation process.

Since the first organ that is formed during organogenesis is the heart, differentiation of mouse embryonic stem cells (D3 pluripotent embryonic stem cell line) into cardiomyocytes *in vitro* has been documented. The *in vitro* process for the differentiation into heart beating cells is well characterised and highly standardised. In the presence of mLIF (mouse leukaemia inhibiting factor) D3 cells can be maintained in the undifferentiated stage as a continuous cell line. In the absence of mLIF the cells will form embryonic bodies that subsequently spontaneously differentiate into functional cardiomyocytes and beating can be observed by simple microscopic evaluation.

Determination of embryotoxicity of selected compounds of the invention is performed by this embryonic stem cell test (EST). Two permanent mouse cell lines are used to assess the embryotoxic potential of test compounds: 3T3 fibroblasts (ATCC CCL-92; ATCC CRL-1658, ATCC CCL-163) and the embryonic stem cell line D3 (ATCC CRL-1934).

Inhibition of differentiation and growth are determined in embryonic stem cells and compared to inhibition of growth in 3T3 fibroblasts, which serves as surrogate for adult cells. Three endpoints are used to classify the embryotoxic potential of test compounds in the EST: Inhibition of growth of embryonic stem cells and 3T3 fibroblasts in MTT assay (MTT cell viability assay kit, Cat.No. 30006, Biotium Inc., www.biotium.com) by 50% of the control (IC50 D3, IC50 3T3) and the inhibition of the differentiation of embryonic stem cells into spontaneously contracting cardiomyocytes by 50% (ID50).

The embryotoxic potential of selected compounds of the invention is determined by ranking experiments in relation to prior art APL.

IV) Anti-bacterial activity assay

Selected compounds of the invention were tested in a bouillon microdilution assay method according to the DIN 58940 (www.din.de) guidelines for determination of susceptibility of bacterial strains with regard to cell growth inhibition. The assay method quantifies bacterial cell growth which corresponds to the turbidity of the liquid culture medium by photometric measurement carried out at 595 nm.

The method of MIC determination was performed according to DIN 58940-5. The volumina were adapted according to the microdilution method as described in DIN 58940-7 guideline.

10

Dependent on water solubility, compounds of the invention were dissolved either in water or ethanol in a concentration of 10mg/ml. Subsequently, the stock was further diluted in water to a concentration of 512µg/ml. The following serial dilutions (factor 2) were performed in water resulting in the following 10 testing concentrations: 256µg/ml, 128µg/ml, 64µg/ml, 32µg/ml, 16µg/ml, 8µg/ml, 4µg/ml, 2µg/ml, 1µg/ml, 0.5µg/ml, 0.25µg/ml and 0.125µg/ml. Diluted compounds of the invention were transferred in 100µl volume to the microtiter plate wells.

15

Bacterial strains were grown in medium dependent on their different requirements and conditions (listed in **Table 8**).

20

Table 8

	Test strain	Typus	Medium	Temp.	Preculture and inoculum	Incub. time
A	<i>Streptococcus pneumoniae</i> DSM 20566 (ATCC 33400)	Gram-positive	CASO Bouillon (Heipha Diagnostika, Cat.No. 5021000)	aerob 37°C +/-2°C	24-48 h pre-culture in CASO Bouillon; 100µl inoculum adjusted to 10 ⁶ microorg/ml	24 h +/- 4h
B	<i>Streptococcus pneumoniae</i> DSM 11967 (ATCC 49619)	Gram-positive	CASO Bouillon	37°C +/-2°C	24-48 h pre-culture in CASO Bouillon; 100µl inoculum adjusted to 10 ⁶ microorg/ml	24 h +/- 4h
C	<i>Enterococcus faecium</i> DSM 20477 (ATCC 19434)	Gram-positive	CASO Bouillon	37°C +/-2°C	24-48 h pre-culture in CASO Bouillon; 100µl inoculum adjusted to 10 ⁶	24 h +/- 4h

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					microorg/ml	
D	<i>Moraxella</i> <i>catarrhalis</i> DMS 11994 (ATCC 43617)	Gram- negative	CASO Bouillon	5% CO ₂ ; 37°C	24-48 h pre- culture in CASO Bouillon; 100µl inoculum adjusted to 10 ⁶ microorg/ml	24 h +/- 4h
E	<i>Bacteroides</i> <i>fragilis</i> DSM 2151 (ATCC 25285)	Gram- negative	CASO Bouillon	without shaking- anaerob; 37°C +/-2°C	24-48 h pre- culture in CASO Bouillon; 100µl inoculum adjusted to 10 ⁶ microorg/ml	24 h +/- 4h

Pre-cultures of bacteria were grown in appropriate liquid media (refer to ATCC
webpage, www.atcc.org) and afterwards were inoculated in corresponding liquid
medium. 100µl of the inoculums [adjusted to an amount of app. 1×10^6 microorganisms
5 per ml (range of 10^5 - 10^8 microorganisms per ml)] were added to each of the testing
compound concentrations and cultivated under the appropriate conditions.

Before and after incubation, bacterial growth was determined by photometric
analysis against a positive control containing growing bacteria without compound and a
10 sterile/negative control containing only the medium. The minimal inhibitory drug
concentration (MIC) is defined as the lowest drug concentration of the dilution series on
which no increase on optical density was observed.

Table 9 [(a) to (e)] displays the results (MIC values in µg/mL) of the anti-bacterial
15 activity assay obtained for selected compounds of the invention (**compounds 2, 3, 67,**
89, 90, 107, 260, 266, 301) against different bacterial species in comparison to prior art
example miltefosine (hexadecyl-phosphocholine).

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Table 9: Susceptibilities of different bacterial species (MICs in µg/mL) to selected alkyl phospholipid derivative compounds

(a)

bacterium	A
2	8
89	8
107	8
miltefosine	128

5

(b)

bacterium	B
2	8
89	4
107	4
miltefosine	128

(c)

bacterium	C
107	8
301	8
miltefosine	32

(b)(d)

bacterium	D
2	4
3	8
67	8
89	4
107	4
260	8
266	8
miltefosine	16

(e)

bacterium	E
3	128
90	128
107	64
266	128
miltefosine	>256

10

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The result presented in **table 9** show the strong antibacterial activity of the selected compounds of the invention against different gram-positive and gram-negative bacteria compared to prior art compound miltefosine (hexadecyl-phosphocholine).

V) Anti-fungal activity assay

Anti-fungal activity of selected compounds of the invention was assessed by means of anti-fungal susceptibility tests as follows.

The antifungal activities of the compounds of the invention against different fungi were measured according to standard broth microdilution methods of the US National Committee for Clinical Laboratory standards (NCCLS) for yeasts (NCCLS document M27-A, 1997) and filamentous fungi (NCCLS document M38-A, 2002).

Compounds of the invention were tested for *in vitro* antifungal activity against different fungal strains (listed in **Table 10**).

Table 10

	Test strain	Morphology	Origin	ATCC Medium	Temp. ATCC
A	<i>Aspergillus fumigatus</i> ATCC 204305	filamentous	ATCC	Malt extract agar Malt extract 20g Glucose 20g Peptone 1g ad aqua dest. 1l	25°C
B	<i>Aspergillus fumigatus</i> 322-384	filamentous	isolate		
C	<i>Aspergillus fumigatus</i> 040-200167	filamentous	isolate		
D	<i>Candida albicans</i> ATCC 10231	yeast	ATCC	Yeast mold broth	25°C
E	<i>Candida albicans</i> ATCC 90028	yeast	ATCC	Yeast mold broth	35°C
F	<i>Candida albicans</i> TS3 (Shrikantha et al., Journal of Bacteriology 2000, 182(6):1580-1591)	yeast	Auxotroph strain of ura 3.	Cells were maintained on agar containing modified Lee's medium supplemented with 0.01mM uridine.	
G	<i>Candida parapsilosis</i> ATCC 22019	yeast	ATCC	Yeast mold broth	35°C
H	<i>Cryptococcus neoformans</i> ATCC 90112	yeast	ATCC	Yeast mold broth	24°C
I	<i>Cryptococcus neoformans</i> H99 (Ganendren et al., Antimicrobial Agents and Chemotherapy, 2004, 48(5):1561-1569)	yeast	Clinical isolate from human cerebrospinal fluid;	RPMI broth medium	
J	<i>Cryptococcus gattii</i> ATCC 32608	yeast	ATCC	Malt agar medium Malt extract 30g Agar, Bacto 15g ad aqua dest 1l; pH 5.5	26°C

Culture conditions of ATCC strains were obtained from the web site (www.atcc.org).

5 Stock solutions of compounds of the invention were freshly prepared on the days of experiments equal to 1.28mg/10ml media. Serial dilutions were performed to achieve the following testing concentrations: 64µg/ml, 32µg/ml, 16µg/ml, 8µg/ml, 4µg/ml, 2µg/ml, 1µg/ml, 0.5µg/ml, 0.25µg/ml and 0.125µg/ml.

An inoculum of 10^6 CFU/ml of the fungi strain was prepared in the appropriate medium and transferred to test tubes for incubation.

10 The method is used to determine the minimum inhibitory concentrations (MIC) of drugs on fungi strains. The MIC was defined by photometric measurement at 595nm after 48h of culture at 35°C at that concentration which demonstrated more than 80% inhibition of visible growth for yeast protocol. For the filamentous fungi protocol, MIC determination took place after 48 to 72 h of culture at 35°C and was defined at that
15 concentration which produced more than 50% visible growth inhibition.

Table 11 displays the results (MIC values in µg/mL) of the anti-fungal activity assay obtained for selected compounds of the invention (**compounds 1, 2, 3, 5, 8, 22**) in comparison to prior art example erucylphosphocholine (ErPC).

Table 11: Susceptibilities of different fungal species (MICs in µg/mL) to selected alkyl phospholipid derivative compounds

fungus	1	2	3	5	8	22	ErPC
A	2	2	3	6	2	3	>64
B	2	2	2	8	2	2	>64
C	4	6	4	24	2	3	>64
D	2	1	1	2	0,75	0,5	>64
E	1	1	1	2	0,75	1	>64
F	1,5	1,5	2	2	1	1	64
G	3	2	2	3	0,75	1	64
H	1,5	1,5	1,5	1,5	2	1,5	4
I	2	1	1	2	1,5	6,6	3
J	1	0,75	0,75	0,75	0,75	0,5	1,5

5

The result presented in **table 11** show the strong antifungal activity of the selected compounds of the invention compared to prior art compound erucylphosphocholine (ErPC).

VI) *In vitro* drug activity assay against different protozoa

In vitro activity of selected compounds of the invention against different protozoa was assessed as follows.

Murine (CD1) peritoneal macrophages were harvested 24 hours after starch
5 induction and dispensed into 96-well plates at a concentration of 4×10^5 mL. After 24 hours, the cells were infected with *Trypanosoma cruzi* Tulahuan LAC-Z amastigotes (grown and cultured according to Buckner et al., *Infection and Immunity* 1999, 67(1): 403-409). 24 hours later, the infected cells were exposed to the test compounds (compounds of the invention as well as known prior art compounds) for 3 days and 50
10 μ L of 500 μ M CPRG-1% Nonidet P-40 was added to each well. The plates were read after 2 to 5 hours at 570 nm (Buckner et al., *Antimicrobial Agents and Chemotherapy* 1996, 40(11): 2592-2597). ED_{50} values were calculated with Mxlfrit (IDBS).

Trypanosoma brucei rhodesiense STIB900 bloodstream form trypomastigotes were maintained in HMI-18 medium (Hirumi H, Hirumi K, *J Parasitol.* 1989, 75(6):985-989)
15 with 15% heat-inactivated fetal calf serum at 37°C, 5% CO₂, humidified atmosphere. Trypomastigotes were washed and resuspended in fresh medium at a concentration of 2×10^5 mL. Test compounds were given to the trypomastigotes and plates were incubated for 72 hours at 37°C, 5% CO₂, humidified atmosphere. At 72 hours the plates were assessed microscopically before Alamar Blue was added (Raz et al., *Acta Trop.* 1997, 68: 139-147). Plates were read after 5 to 6 hours at EX/EM 530/585 nm
20 with a filter cutoff at 550 nm. ED_{50} values were calculated with Mxlfrit (IDBS).

Plasmodium falciparum strain K1 and strain 3D7 parasites were cultured according to Trager W and Jensen JB (*Science* 1976, 193: 673-675). *In vitro* drug susceptibility assays with the test compounds were carried out according to Korsinczky M et al.
25 (Antimicrobial agents and chemotherapy 2000, 44(8): 2100-2108) and Fivelman QL et al. (Antimicrobial agents and chemotherapy 2004, 48(11): 4097-4102) using a ³[H]-hypoxanthine radioisotope method. ED_{50} values were calculated with Mxlfrit (IDBS).

The following protozoa were assessed:

A) *Trypanosoma cruzi* (Tulahuan-LACZ amstigotes in PEM, Lorente SO et al.,
30 Antimicrobial agents and chemotherapy 2004, 48(8): 2937-2950; Buckner et al., *Infection and Immunity* 1999, 67(1): 403-409; Buckner et al., *Antimicrobial Agents and Chemotherapy* 1996, 40(11): 2592-2597)

B) *Trypanosoma brucei rhodesiense* (strain STIB900, Lorente SO et al.,

Antimicrobial agents and chemotherapy 2004, 48(8): 2937-2950; Habtemariam S, BMC Pharmacology 2003, 3:6)

- 5 **C)** Plasmodium falciparum (strain K1, Korsinczky M et al., Antimicrobial agents and chemotherapy 2000, 44(8): 2100-2108; Thaitong S and Beale GH, Trans. R. Soc. Trop. Med. Hyg. 1981, 75: 271-273; Trager W and Jensen JB, Science 1976, 193: 673-675)

- D)** Plasmodium falciparum (strain 3D7, Mu et al., PLoS Biology 2005, 3(10): e335)

10 Following **table 12** displays the results (ED₅₀ values in µg/mL) of the *in vitro* activity assay obtained for selected compounds of the invention (**compounds 1, 2, 3, 4, 5**) against different protozoa.

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Table 12: *In vitro* drug activity assay results for different protozoa (ED₅₀ values for a number of selected exemplary compounds)

compound	protozoon	ED ₅₀ (µg/mL)
1	A	1,71
1	B	18,80
1	C	6,93
1	D	9,97
2	A	0,50
2	B	17,50
2	C	19,36
2	D	2,21
3	A	0,33
3	B	25,03
3	C	8,03
3	D	2,25
4	A	1,93
4	B	12,29
4	C	5,44
4	D	15,32
5	A	1,43
5	B	14,20
5	C	21,26
5	D	16,31
benznidazole	A	0,22
miltefosine	A	0,63

VII) *In vitro* activity of Miltefosine and Benznidazole against Trypanosoma cruzi

In vitro activity of Miltefosine and Benznidazole in the course of a combination treatment against Trypanosoma cruzi strain Y was assessed compared to the respective single treatments with miltefosine or benznidazole alone.

5

Miltefosine and Benznidazol were tested *in vitro* in combination against epimastigote forms of Trypanosoma cruzi strain Y which were isolated from a chagasic patient in Sao Paulo, Brazil and obtained from Dr. Victor Nussenzweig (Silva, LH. and Nussenzweig, V.; Folia clin. biol., 20: 191-207, 1953). This T. cruzi Y strain can also be ordered at ATCC 50832, while the ATCC strain must be re-adapted by several passages through mice in order to regain the strain's original characteristics of differentiation and virulence.

Epimastigotes were axenially cultured in brain heart infusion medium (BHI, Becton, Dickinson, Cat.No. 221812) supplemented with 10mg of hemin per liter and 5% heat inactivated fetal calf serum (FCS) at 28°C with shaking (~ 80rpm) up to a maximum of 10-12 passages, before the cultures were aged to obtain metacyclics that were purified on a DE-52 column (Whatman DEAE cellulose ion exchange column, Waco, Cat.No. 17050-03 or 17050-04) and injected into mice. After 2-4 weeks parasites were recovered from blood and placed back into axenic culture.

Stock solutions of Miltefosine and Benznidazol in concentrations of 10mg/ml and 20mg/ml dissolved in methanol were used. Stock solutions were serially diluted with a factor of 2 in BHI-FCS medium. For Benznidazol the following testing concentrations were used: 80µg/ml, 40µg/ml, 20µg/ml, 10µg/ml, 5µg/ml and 2.5µg/ml. The testing concentrations for Miltefosine were 20µg/ml, 10µg/ml, 5µg/ml, 2.5µg/ml, 1.25µg/ml and 0.625µg/ml.

2x10⁶ epimastigotes were incubated in BHI-FCS medium with Miltefosine and Benznidazol in a final volume of 200µl. After 72h incubation at 28°C, parasite growth was determined by direct counting the number of parasites with a Neubauer chamber. The 50% inhibitory concentrations were determined by linear regression analysis.

30

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For combination *in vitro* testing of Miltefosine and Benznidazol against amastigote/trypomastigote forms, *in vitro* differentiation of epimastigotes into metacyclic trypomastigote forms was achieved using a chemically defined triatomine artificial urine medium. Trypanosoma cruzi cultures grown in liver infusion tryptose medium (LIT, Castellani et al., J. Protozool. 1967, 14(3): 447-451) at 27°C and
5 containing approximately 100% of epimastigotes at the end of the exponential phase were centrifuged at 10 000 x g for 15min at 10°C and resuspended in artificial triatomine urine (TAU) (190 mM NaCl, 8 mM phosphate buffer pH 6.0, 17 mM KCl, 2 mM CaCl₂, 2 mM MgCl₂). The parasites were diluted to a final concentration of 3-5 x
10 10⁶ parasites/ml in TAU medium supplemented with 2.5% (v/v) sodium bicarbonate 1.4%, 500 U penicillin/ml, 10 mM L-Proline and incubated at 27°C in tightly closed culture flasks for 2 h at room temperature. The flasks had a liquid depth not exceeding 10mm and were incubated without agitation.

Excudate cells removed from the peritoneal cavities of BALB/c mice were cultured
15 in complete RPMI 1640 medium (Difco) containing 2 mM L-glutamine, 1 mM sodium pyruvate, 10µg/ml gentamicin, minimal essential medium with nonessential amino acids, 10mM HEPES, 50 µM 2-mercaptoethanol and 5% FCS. 3x10⁵ cells/ml were seeded on 24 well plates. Murine peritoneal macrophages were infected with 1.5 x 10⁶ metacyclic trypomastigotes at a ratio of 5 parasites per macrophage per well. After 24h
20 non-internalized parasites were removed and infected macrophages were cultured in a volume of 1ml in complete RPMI medium alone, medium with 10ng/ml LPS and 40 U/ml IFN-gamma or medium containing testing compounds.

Miltefosine and Benznidazol were diluted in complete RPMI medium. The testing concentrations for Benznidazol were 40µg/ml, 20µg/ml, 10µg/ml, 5µg/ml, 2.5µg/ml and
25 1.25µg/ml. For Miltefosine the following testing concentrations were used: 40µg/ml, 20µg/ml, 10µg/ml, 5µg/ml, 2.5µg/ml, 1.25µg/ml and 0,625 µg/ml.

After incubation at 37°C and 5% CO₂, motile trypomastigotes were counted in the supernatants of cultures after 5, 7 and 10 days of infection. To assess the number of intracellular amastigotes, macrophages were plated onto 13 mm² coverslips in 24 well
30 plates and infected with 1.5 x 10⁶ metacyclic trypomastigotes. After 3 days of culture, the monolayers of infected macrophages were washed with phosphate buffered saline (PBS) at 37°C, fixed in methanol and stained with Giemsa. The numbers of amastigotes were determined by counting at least 400 macrophages in duplicate

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cultures. The readout was the average number of amastigotes per infected macrophage.

Following **table 13** displays the results of the *in vitro* activity assay obtained for
 5 benznidazole, miltefosine and a combination of benznidazole + miltefosine in different concentrations against epimastigotes of *Trypanosoma cruzi* strain Y.

Table 13

	Drug concentration [ug/mL]	Epimastigotes [amount/mL]
benznidazole	5	455.833
Miltefosine	1,25	820.000
benznidazole + miltefosine	5 + 1,25	233.333
benznidazole	10	358.333
Miltefosine	2,5	290.000
benznidazole + miltefosine	10 + 2,5	40.833
benznidazole	40	190.000
Miltefosine	1,25	820.000
benznidazole + miltefosine	40 + 1,25	81.000

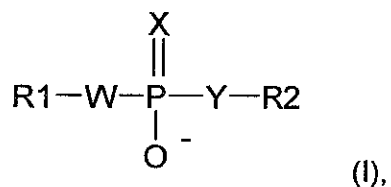
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The result presented in **table 13** clearly demonstrate the strong synergistic effect achieved through the administration of benznidazole + miltefosine in different drug concentrations compared to the single administration of the respective drug.

15

Claims

1. Use of an alkyl phospholipid derivative according to formula (I)



wherein:

W, X, Y independently are selected from the group consisting of: "oxygen atom, sulphur atom";

R1 is -R5;

R2 is -R8;

R5 is independently selected from the group consisting of: substituted or unsubstituted C8-C30 "alkyl" ", where "alkyl" stands for acyclic and cyclic saturated, unsaturated or partially unsaturated hydrocarbons which may be straight chain, branched or cyclic, and cyclic hydrocarbons as part of a straight-chain or branched hydrocarbon system and which may contain one or more double and/or triple bonds;

R8 is selected from the group consisting of: "substituted or unsubstituted heterocycle", where heterocycle is

- (i) a 5-, 6- or 7-membered saturated, partially unsaturated or aromatic monocyclic carbon atom ring system with at least one heteroatom selected from the group consisting of: "nitrogen atom, oxygen atom, sulphur atom, arsenic atom", and with the proviso that at least one heteroatom is a quaternary nitrogen atom or a quaternary arsenic atom,

where two or more ring atoms of heterocycle can be additionally linked via an alkylene-bridge, and where heterocycle if substituted is substituted with at least one radical R12, which in case of two or more radicals R12 are independently from each other identical, partly identical or different;

R12 is independently from each other selected from the group consisting of: "hydrogen atom, substituted or unsubstituted C1-C18 "alkyl", substituted or unsubstituted "C3-C8 cycloalkyl", substituted or unsubstituted (C1-C12 "alkyl")_s-B-(C1-C12 "alkyl")_t-D-(C1-C12"alkyl")_u, substituted or unsubstituted "aryl", substituted or unsubstituted "heteroaryl", substituted or unsubstituted "alkoxy", -OH, halogen, -F, -Cl, -Br, -I, =O, -C(O)O-(C1-C12 "alkyl"), -C(O)O-(C3-C8 cycloalkyl)", -C(O)O-"aryl", -C(O)O-"heteroaryl", -C(O)O-"heterocyclyl", -C(O)-(C1-C12 "alkyl"), -C(O)-(C3-C8 "cycloalkyl"), -C(O)-"aryl", -C(O)-"heteroaryl", -C(O)-"heterocyclyl" ", and

optionally two substituents R12 can together form a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms;

where "alkyl" has the meaning defined above; "C3-C8 cycloalkyl" stands for a saturated or partially unsaturated non-aromatic cyclic hydrocarbon group containing 3 to 8 carbon atoms that may optionally be linked via an "alkyl" group, in which the "alkyl" group has the meaning defined above; "aryl" stands for aromatic systems having 3 to 14 carbon atoms, including systems in which the aromatic cycle is part of a bi-or polycyclic saturated, partially unsaturated and/or aromatic system; "heteroaryl" stands for a 5-, 6- or 7-membered cyclic aromatic radical which comprises at least 1 heteroatom; "alkoxy" stands for radicals in which an "alkyl" group as defined above, a "C3-C8 cycloalkyl" as defined above, an "aryl" group as defined above, a "heteroaryl" group as defined above and/or a "heterocyclyl" group is linked via an oxygen atom, in which the "heterocyclyl" group stands for a mono- or polycyclic system of 3 to 20 ring atoms which may be unsaturated, mono- or poly unsaturated but may not be aromatic;

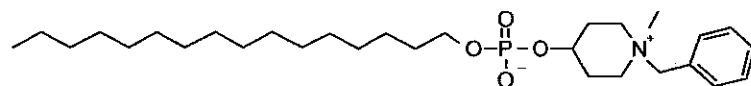
B, D are independently from each other selected from the group consisting of "oxygen atom; sulphur atom; S(O₂)";

s, t, u independently from each other are 0 or 1;

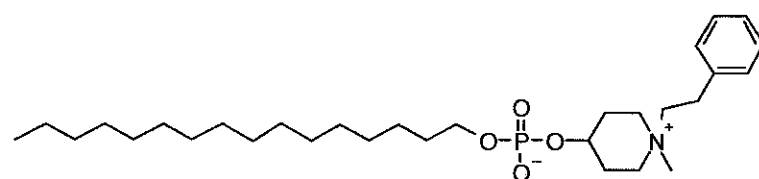
for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals selected from the group consisting of aspergillosis, blastomycosis, candidiasis, chromoblastomycosis, coccidioidomycosis, cryptococcosis, dermatomycosis, dermatophytosis, histoplasmosis, lobomycosis, mucormycosis, mycetoma, mycotic keratitis, oculomycosis, onychomycosis, otomycosis, paracoccidiomycosis, phaeohyphomycosis, piedra, pityriasis versicolor, rhinosporidiosis, sporotrichosis, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea favosa, tinea nigra, tinea pedis, tinea unguium, zygomycosis.

2. The use as claimed in claim 1, where the alkyl phospholipid derivative is selected from the group consisting of:

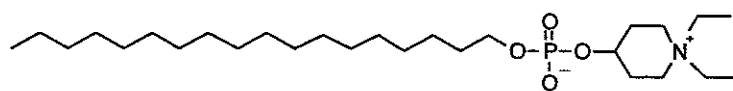
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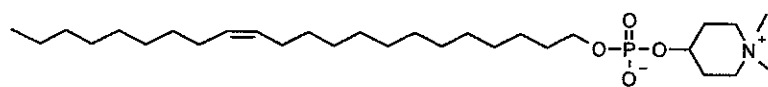
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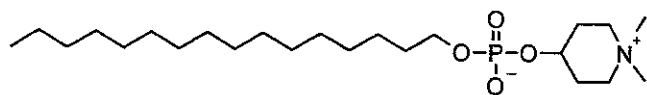
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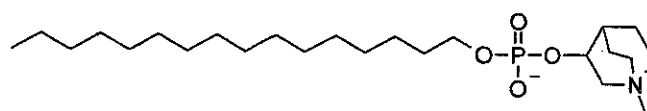
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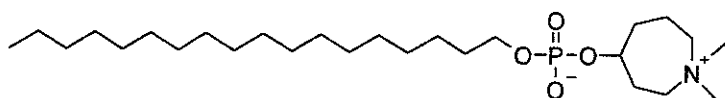
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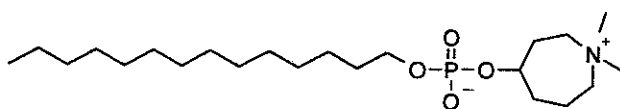
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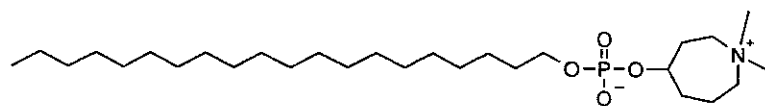
Compound 83



Compound 85

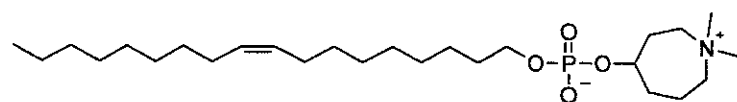


Compound 86



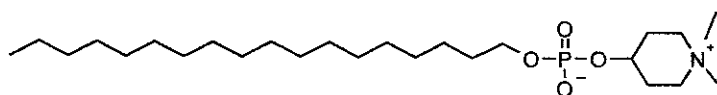
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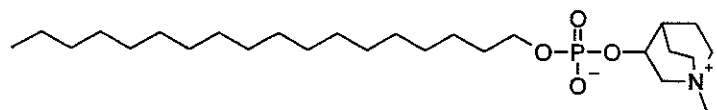
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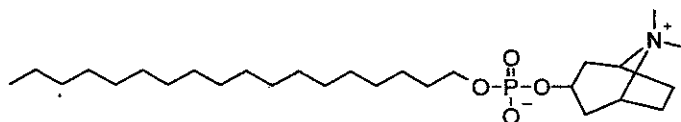
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Compound 103



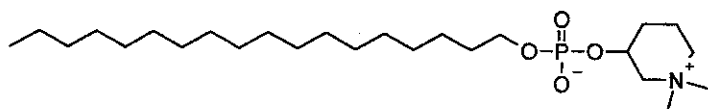
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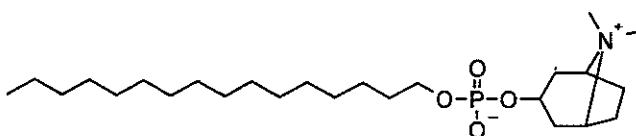


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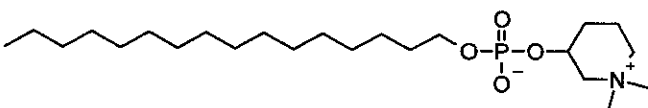
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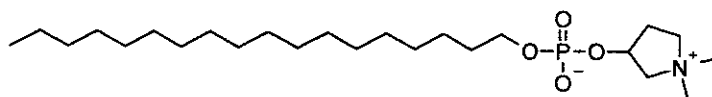
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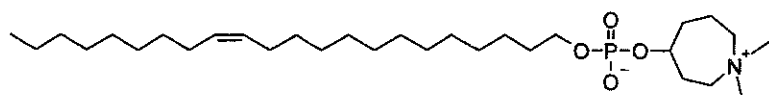
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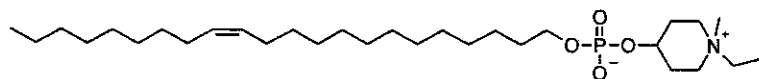
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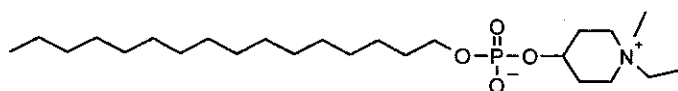
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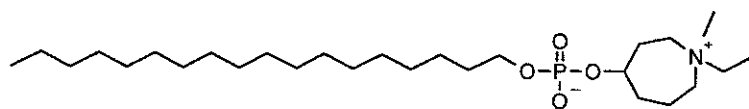
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Compound 138

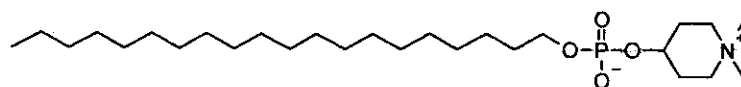


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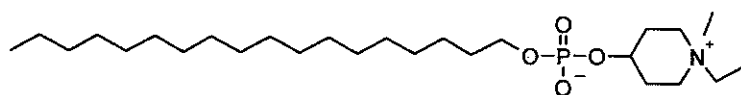
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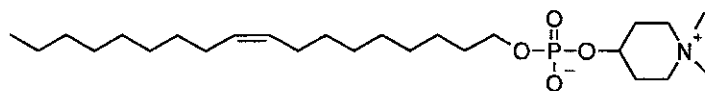


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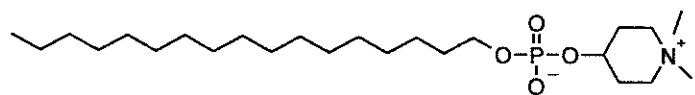


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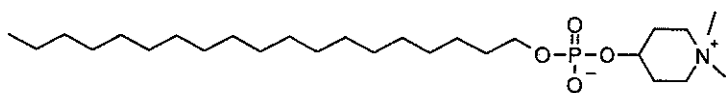


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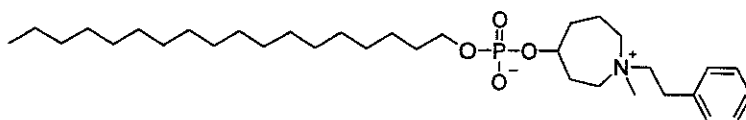
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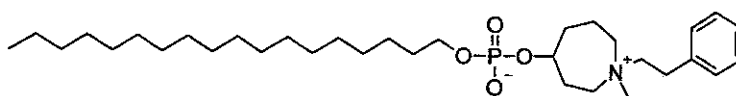
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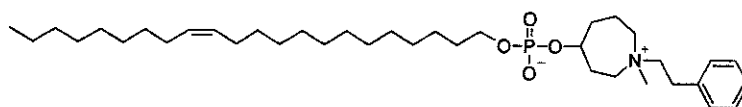
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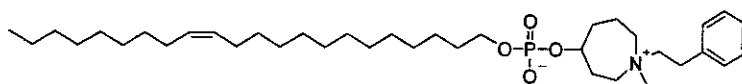
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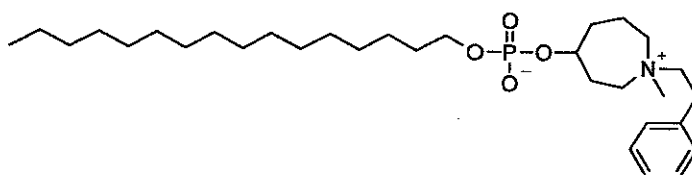
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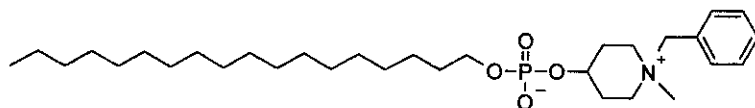
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Compound 187

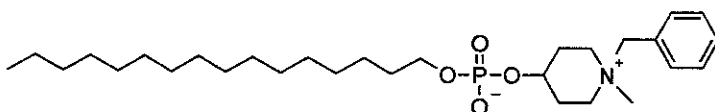


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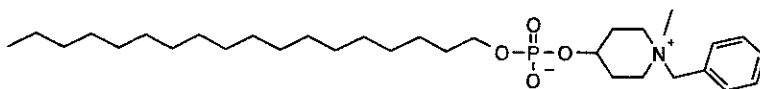
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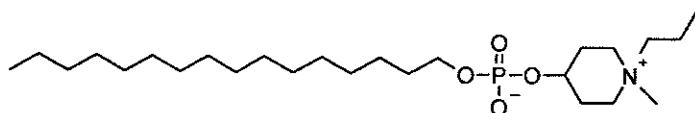
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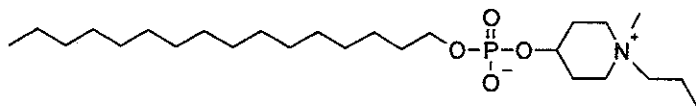
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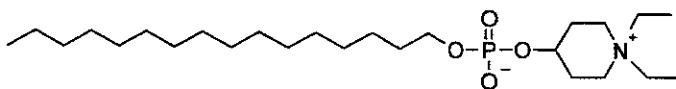


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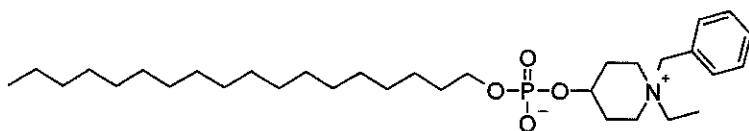
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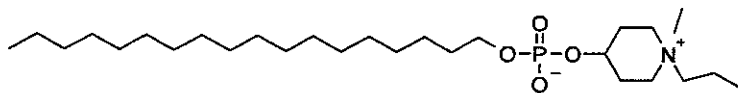
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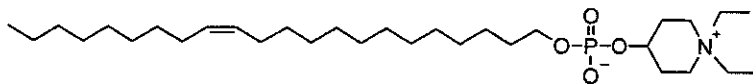
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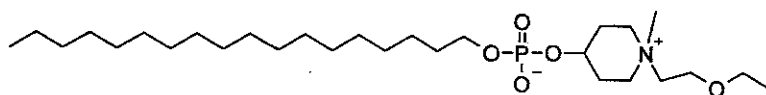
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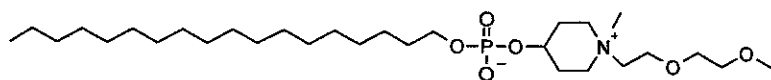
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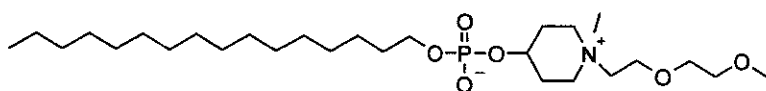
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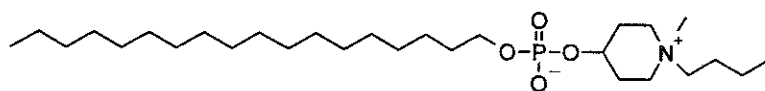
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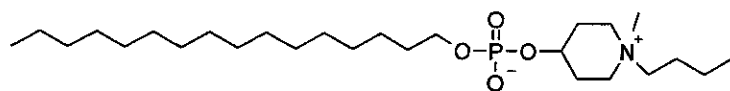
Compound 214



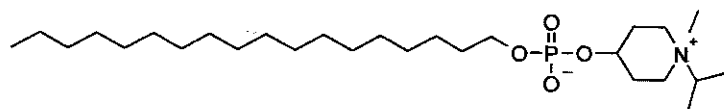
Compound 215



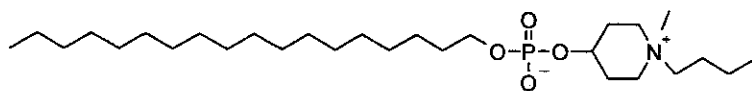
Compound 216



Compound 217

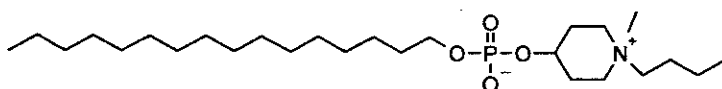


Compound 218



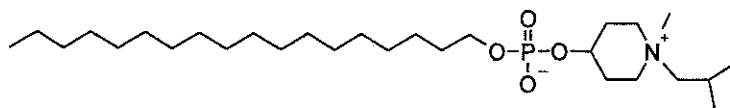
;

Compound 219



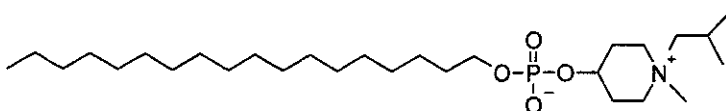
;

Compound 220



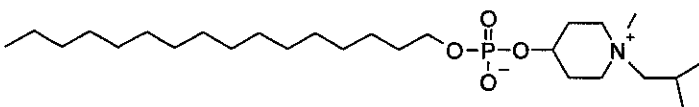
;

Compound 221



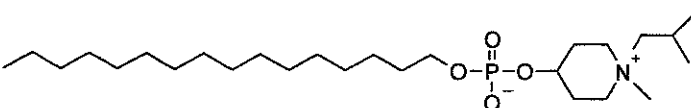
;

Compound 222



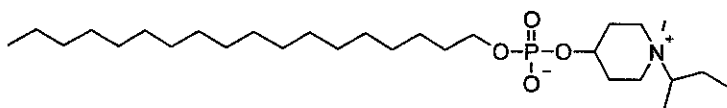
;

Compound 223

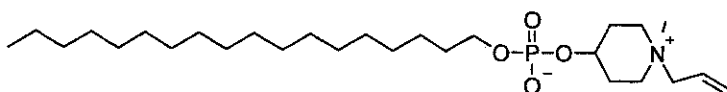


;

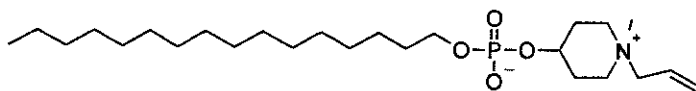
Compound 226



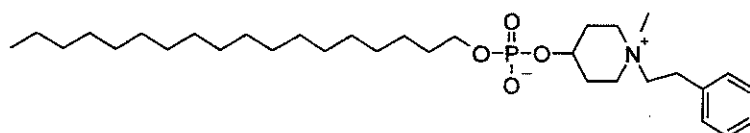
Compound 228



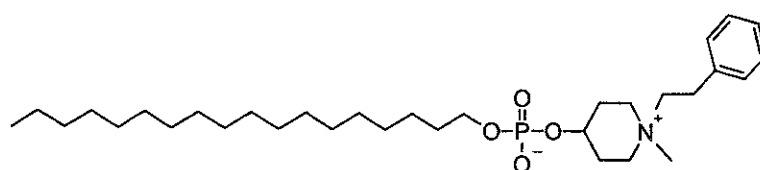
Compound 229



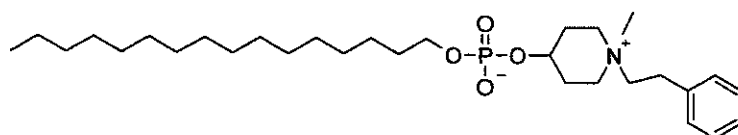
Compound 230



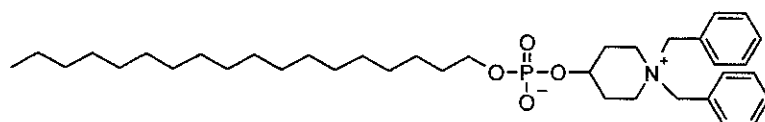
Compound 231



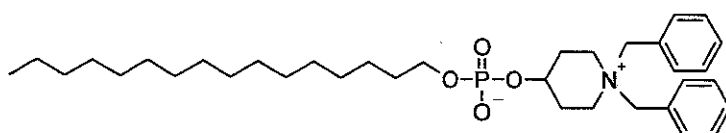
Compound 232



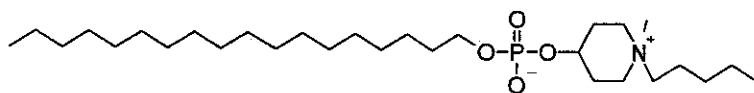
Compound 233



Compound 234

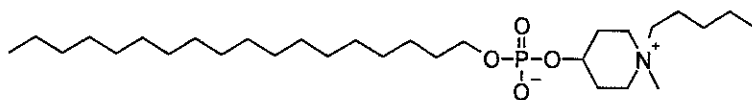


Compound 247



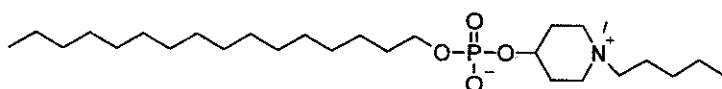
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Compound 248



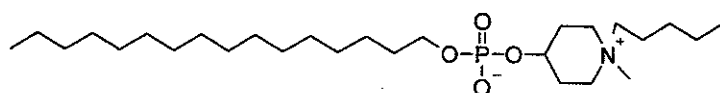
;

Compound 249



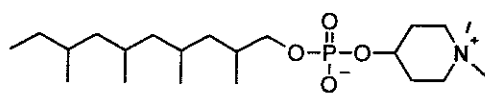
;

Compound 250

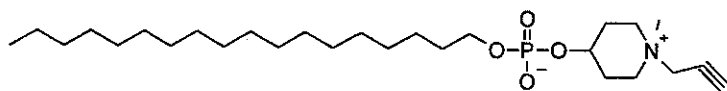


;

Compound 258

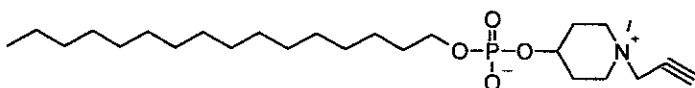


Compound 261



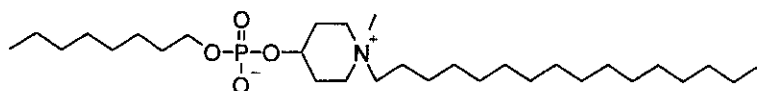
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Compound 262



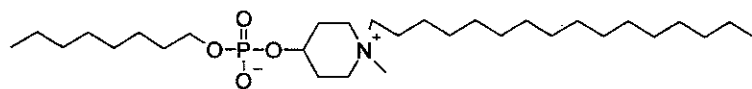
;

Compound 264



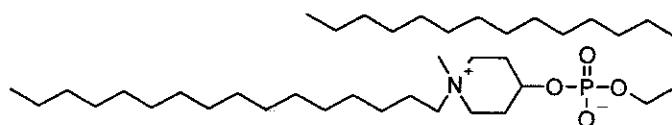
;

Compound 265

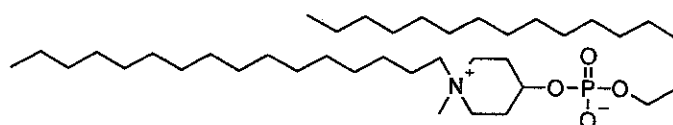


;

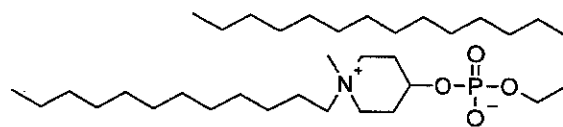
Compound 269



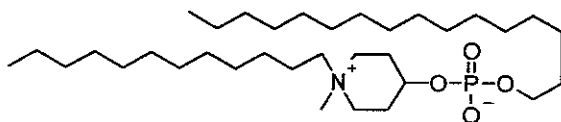
Compound 270



Compound 271

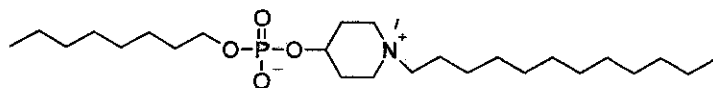


Compound 272

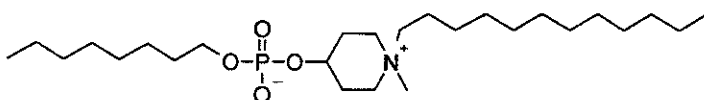


;

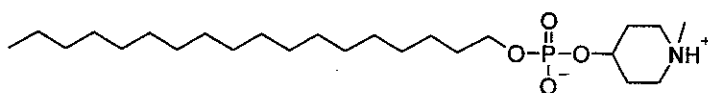
Compound 279



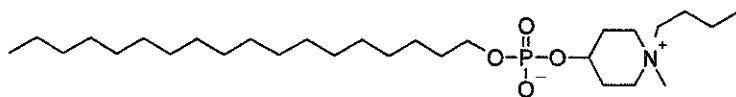
Compound 280



Compound 282

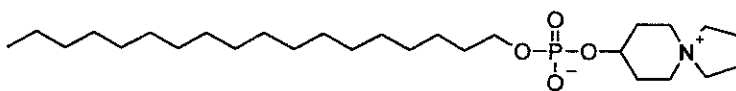


Compound 293



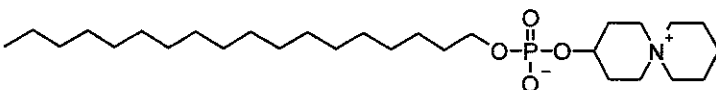
;

Compound 296



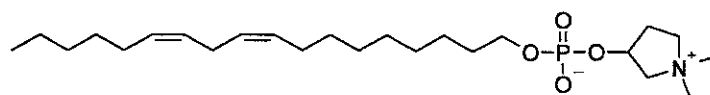
;

Compound 297



;

Compound 302



;

3. The use as claimed in claim 2, where the alkyl phospholipid derivative is selected from the group consisting of: "**Compound 1, 4, 5, and/or compound 17**".

4. The use as claimed in any of claims 1 to 3, where the mammal is selected from the group consisting of "human, domestic animals, cattle, livestock, pets, cow, sheep, pig, goat, horse, pony, donkey, hinny, mule, hare, rabbit, cat, dog, guinea pig, hamster, rat, mouse" and preferably is human.
5. The use as claimed in any of claims 1 to 4, where such medicament comprises at least one additional pharmacologically active substance.

6. The use as claimed in claim 5, where the at least one additional pharmacologically active substance is selected from the group consisting of; amphotericin B [(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-mannopyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]-nonatriaconta-19, 21, 23, 25, 27, 29, 31-heptaene-36-carboxylic acid]; liposomal amphotericin B, and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine]".
7. The use as claimed in any of claims 5 to 6, where the alkyl phospholipid derivative is selected from the group consisting of perifosine (octadecyl-1,1-dimethyl-piperidino-4-yl-phosphate) and the at least one additional pharmacologically active substance is selected from the group consisting of amphotericin B [(1R, 3S, 5R, 6R, 9R, 11R, 15S, 16R, 17R, 18S, 19E, 21E, 23E, 25E, 27E, 29E, 31E, 33R, 35S, 36R, 37S)-33-[(3-Amino-3,6-dideoxy-beta-D-mannopyranosyl)oxy]-1, 3, 5, 6, 9, 11, 17, 37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]-nonatriaconta-19, 21, 23, 25, 27, 29, 31-heptaene-36-carboxylic acid]; liposomal amphotericin B, and/or paromomycin [O-2-amino-2-deoxy-alpha-D-glucopyranosyl-(1-4)-O-[O-2,6-diamino-2,6-dideoxy-beta-L-idopyranosyl-(1-3)-beta-D-ribofuranosyl-(1-5)]-2-deoxy-D-streptamine]".