



(43) International Publication Date  
7 August 2014 (07.08.2014)

(10) International Publication Number  
**WO 2014/118361 A1**

(51) International Patent Classification:

*A61K 31/16* (2006.01) *C07C 231/00* (2006.01)  
*A61K 31/165* (2006.01) *C07C 233/58* (2006.01)  
*A61K 31/166* (2006.01) *C07C 233/64* (2006.01)  
*A61K 31/167* (2006.01) *C07C 235/46* (2006.01)  
*A61K 31/4965* (2006.01) *A61P 31/00* (2006.01)  
*C07D 241/02* (2006.01)

(21) International Application Number:

PCT/EP2014/052012

(22) International Filing Date:

3 February 2014 (03.02.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

13153813.4 4 February 2013 (04.02.2013) EP

(71) Applicant: **BIOVERSYS AG** [CH/CH]; Hochbergerstrasse 60c, CH-4057 Basel (CH).

(72) Inventors: **SCHNEIDER, Peter**; Bäumliackerstrasse 8, CH-4103 Bottmingen (CH). **RIEDL, Rainer**; Hungerstrasse 49, CH-8832 Wilen bei Wollerau (CH). **TIGGES, Marcel**; Tulpenweg 11, CH-4153 Reinach (CH). **GITZINGER, Marc**; Grendelweg 21, CH-5047 Eiken (CH). **PIEREN, Michel**; Schafmattweg 27, CH-4102 Binningen (CH). **LEVI, Assaf**; Reichensteinerstrasse 29, CH-4053 Basel (CH). **SEPHTON, Mark**; 67 High Street, Great Abington, Cambridge Cambridgeshire CB21 6AB (GB). **SCHELLHORN, Birgit**; Hermann Währer Strasse 50, 79576 Weil am Rhein (DE). **ZUEGER, Patrik**; Moosstrasse 1, CH-8134 Adliswil (CH). **BRAND, Michael**; Rebenweg 4, CH-5603 Staufen (CH). **GYGAX,**

**Daniel**; Wulliweg 357, CH-4204 Himmelried (CH). **SPIES, Peter**; Blauenstrasse 5, CH-4222 Zwingen (CH).

(74) Agent: **BECKER, Konrad**; Latscha Schöllhorn Partner AG, Aeschenvorstadt 55, CH-4051 Basel (CH).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

(54) Title: COMPOSITION FOR TREATMENT OF PATHOGENS THAT ARE RESISTANT TO TETRACYCLINES

(57) Abstract: The invention relates to compounds and pharmaceutical compositions useful in combination with tetracyclines in the treatment of bacterial infections caused by Gram-positive and Gram-negative pathogens, with particular efficacy in tetracycline resistant strains. These compounds specifically bind to TetR and therefore prevent the transcriptional activation of tet resistance genes. The compounds have a potentiating effect on the activity of members of the tetracycline family, in particular of tetracycline, minocycline, doxycycline and tigecycline, in the treatment of tetracycline susceptible, intermediate and tetracycline resistant pathogens.



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## COMPOSITION FOR TREATMENT OF PATHOGENS THAT ARE RESISTANT TO TETRACYCLINES

### Field of the invention

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The invention relates to compounds and pharmaceutical compositions useful in combination with tetracyclines in the treatment of bacterial infections caused by Gram-positive and Gram-negative pathogens, with particular efficacy in tetracycline resistant strains. The invention further relates to a method of treating bacterial infections.

10

### Background of the invention

The global problem of antimicrobial resistance is well recognized by national authorities and rated as a major threat of the 21<sup>st</sup> century (for a review see Boucher H. et al., *Clinical Infectious Diseases* 2009, 48(1), 1-12). In contrast to *de novo* antibiotic development, efforts on alternative approaches such as antibiotic potentiators – following the Augmentin paradigm – have been intensified. The pathogens that cause major problems especially in hospital environments are often summarized as ESKAPE group of opportunistic bacteria (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (Rice L., *The Journal of Infectious Diseases* 2008, 197(8), 1079-1081), which needs to be expanded with *Clostridium difficile*. Multi-resistant or extensively drug resistant isolates belonging to this group are increasingly hard to treat, and there exists a raising number of untreatable strains. The only limiting factor in treatment of these pathogens with the existing portfolio of antibiotics is the antimicrobial resistance. Antibiotics that have been prescribed by physicians for decades due to their preferable efficacy or toxicity profile thus had to be largely replaced.

Tetracyclines are proven antibacterial agents and represent one of the most trusted classes of antibiotics. Discovered in the 1940s, the tetracyclines are a family of antibiotics that inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site (Griffin M.O. et al., *American Journal of Physiology. Cell Physiology* 2010, 299(3), C539-48).

The tetracycline class of antibiotics comprises a distinct family of substituted tetracyclic hydronaphthalene compounds produced by strains of *Streptomyces aureofaciens* and *Streptomyces rimosus*. First generation tetracyclines such as tetracycline,

chlortetracycline, oxytetracycline, and demeclocycline are obtained by biosynthesis. Second generation tetracyclines such as doxycycline, lymecycline, meclocycline, methacycline, minocycline, and rolitetracycline are derivatives obtained by semi-synthesis. Third generation tetracyclines such as tigecycline (Tygacil® Pfizer), pentacycline  
5 antibacterials (a structural modification of doxycycline with five rings), azatetracyclines and fluorocyclines (heteroatoms inserted into the D ring), and alkylaminotetracycline antibacterials, are obtained by total synthesis. Although some researchers consider tigecycline to be distinct from other tetracyclines drugs and representing a new family of antibacterials called glycylcyclines, these glycylcyclines are considered tetracyclines for  
10 the purpose of the present invention.

Tetracyclines display broad spectrum bacteriostatic activity in Gram-negative and Gram-positive pathogens. Today, there are 61 tetracycline resistance genes sequenced, which are often located on mobile elements and encode for three major mechanisms of  
15 resistance: i) tetracycline efflux, ii) ribosomal protection, and iii) tetracycline modification (Thaker M. et al., *CMLS* 2010, 67(3), 419-31).

i) Tetracycline efflux proteins belong to the major facilitator superfamily and are found in both Gram-positive and Gram-negative bacteria. According to their sequence homology,  
20 the efflux proteins are divided into 5 groups: Group 1: Tet(A), Tet(B), Tet(C), Tet(D), Tet(E), Tet(G), Tet(H), Tet(J), Tet(Z), and Tet(30); Group 2: Tet(K) and Tet(L); Group 3: Otr(B) and Tcr(3); Group 4: TetA(P); Group 5: Tet(V); and the non-classified Tet(31), Tet(33), Tet(V), Tet(Y), Tet(34), and Tet(35).

25 ii) Ribosomal protection proteins share homology with the elongation factors EF-Tu and EF-G and cause a change in conformation of the ribosome after binding, thus preventing tetracycline binding. Members of ribosomal protection proteins are: Tet(M), Tet(O), Tet(S), Tet(W), Tet(32), Tet(36), Tet(Q), Tet(T), Otr(A), and TetB(P).

30 iii) Tetracycline modification proteins include the enzymes Tet(37) and Tet(X), both of which inactivate tetracycline.

The expression of several of these tet genes is controlled by a family of tetracycline transcriptional regulators known as TetR. TetR family regulators are involved in the  
35 transcriptional control of multidrug efflux pumps, pathways for the biosynthesis of antibiotics, response to osmotic stress and toxic chemicals, control of catabolic pathways, differentiation processes, and pathogenicity (Ramos J.L. et al., *Microbiology and*

*Molecular Biology Reviews* 2005, 69(2), 326-356). The TetR proteins identified in over 115 genera of bacteria and archaea share a common helix-turn-helix (HTH) structure in their DNA-binding domain. However, TetR proteins can work in different ways: they can bind a target operator directly to exert their effect (e.g. TetR binds Tet(A) gene to repress it in the absence of tetracycline), or they can be involved in complex regulatory cascades in which the TetR protein can either be modulated by another regulator, or TetR can trigger the cellular response. Most of the defense mechanisms have only transient benefit that is coupled to an associated biological cost. Thus, resistance gene expression is often tightly regulated at the transcriptional or translational level and often triggered by the antibiotic itself.

In the absence of the antibiotic (or antibiotic induced stress signals), the repressor protein is bound to its cognate operator sequence and therefore repressing the transcription of resistance genes. Addition of the antibiotic removes the transcriptional block with subsequent expression of resistance genes.

A Transcriptional Regulator Inhibitory Compound (TRIC) is predicated on the identification of small inhibitory compounds that efficiently block the function of bacterial resistance genes at the highest-possible level, i.e. their transcription. At this point, in general two different interventions exist: (i) inhibitory binding of an activator to its cognate sequence and (ii) constant binding of a repressor to the DNA. Most of the bacterial resistance pathways follow the repressor model (ii), where activation of resistance genes only occurs when the repressor is removed from the DNA.

## **Summary of the invention**

The invention relates to TetR binding compounds and pharmaceutical compositions comprising these, useful in combination with tetracyclines in the treatment of bacterial infections caused by Gram-positive and Gram-negative pathogens, with particular efficacy in tetracycline resistant strains. These compounds specifically bind to TetR and therefore prevent the transcriptional activation of tet resistance genes. The compounds have a potentiating effect on the activity of members of the tetracycline family, in particular of tetracycline, minocycline, doxycycline and tigecycline, in the treatment of tetracycline susceptible, intermediate and tetracycline resistant pathogens.

In particular the invention relates to pharmaceutical compositions comprising compounds of formula (1), (2), (3) or (4), which are derivatives of a hydroquinone incorporating a

benzamide or related carboxamide function, and one or more tetracyclines. Furthermore the invention relates to novel compounds of formula (1), (2), (3) and (4) as such, and to pharmaceutical compositions comprising compounds of formula (1), (2), (3) or (4).

- 5 Furthermore the invention relates to a method of treating bacterial infections comprising administering to a patient in need thereof a therapeutically effective amount of a mixture of a compound of formula (1), (2), (3) or (4) with one or more tetracyclines.

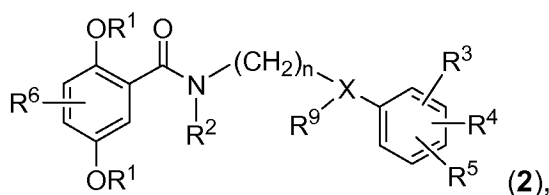
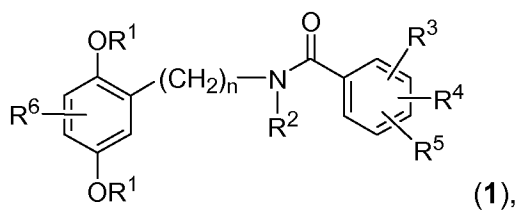
### Detailed description of the invention

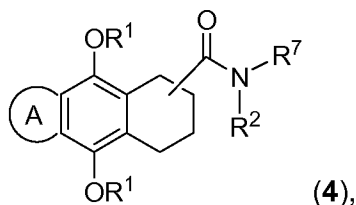
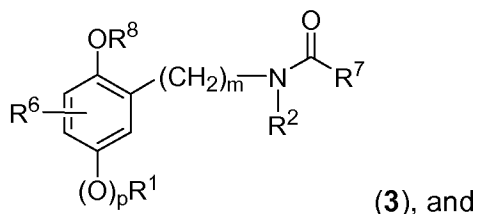
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The invention relates to TetR binding compounds and pharmaceutical compositions comprising these. In particular, the invention relates to pharmaceutical compositions comprising a compound of formula (1), (2), (3) or (4), to such pharmaceutical compositions further comprising one or more tetracyclines. and to novel compounds of  
 15 formula (1), (2), (3) and (4) as defined hereinafter. The invention is based on the observation that a compound preventing TetR from dissociation of the *tetO* operator sequence in the presence of the inducing antibiotic tetracycline or another member of the tetracycline family of antibiotics, for example minocycline or doxycycline, substantially increases the activity of the corresponding tetracyclines in clinical isolates of  
 20 *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*.

In particular the invention relates to pharmaceutical compositions comprising TetR binding compounds of formula

25





5 wherein

R<sup>1</sup> is hydrogen or methyl;

R<sup>2</sup> is hydrogen or methyl;

R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are, independently of each other, hydrogen, lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, halo-lower alkoxy, phenoxy, amino, lower  
10 alkylamino, di-(lower alkyl)amino, optionally substituted lower alkylcarbonylamino, carboxy, lower alkylcarbonyl, lower alkoxy, carbonyl, phenylcarbonyl, or phenyl;

R<sup>6</sup> is hydrogen, phenoxy or phenyl;

R<sup>7</sup> is alkyl, cyclohexyl-lower alkyl, optionally substituted phenyl or phenyl-lower alkyl, or optionally substituted heteroaryl or heteroaryl-lower alkyl;

15 R<sup>8</sup> is hydrogen, methyl, phenyl or halophenyl;

A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the A ring connection, or absent;

X is CH or N;

R<sup>9</sup> is hydrogen or methyl, if X is CH; or R<sup>2</sup> and R<sup>9</sup> together represent ethylene, if X is N;

20 n is 1, 2, 3 or 4;

m is 0 or 1; and

p is 0 or 1.

25 More particularly, the invention relates to compounds of formula (2), (3) and (4) as defined hereinbefore.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

30 The prefix "lower" denotes a radical having up to and including a maximum of 7,

especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

Where the plural form is used for compounds, salts, and the like, this is taken to mean  
5 also a single compound, salt, or the like.

The invention relates also to possible tautomers of compounds of formula (1), (2), (3) or (4).

10 Alkyl has from 1 to 12, preferably from 1 to 7 carbon atoms, and is linear or branched. Alkyl is preferably lower alkyl.

Lower alkyl has 1 to 7, preferably 1 to 4 carbon atoms and is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl. Preferably  
15 lower alkyl is C<sub>1</sub>-C<sub>4</sub>-alkyl, in particular methyl or ethyl.

In optionally substituted phenyl, substituents are preferably lower alkyl, halo-lower alkyl, lower alkoxy-lower alkyl, hydroxy, lower alkoxy, halo-lower alkoxy, lower alkoxy-lower alkoxy, methylenedioxy, hydroxysulfonyloxy, phenoxy, halophenoxy, carboxy, lower  
20 alkoxy-carbonyl, aminocarbonyl, hydroxysulfonyl, aminosulfonyl, phenyl, halophenyl, hydroxyphenyl, halo, cyano or nitro, in particular lower alkyl, halo-lower alkyl, hydroxy, lower alkoxy, phenoxy, halophenoxy, phenyl or halo.

Halophenyl is preferably fluoro- or chlorophenyl, in particular p-chlorophenyl.  
25

Heteroaryl represents an aromatic group containing at least one heteroatom selected from nitrogen, oxygen and sulfur, and is mono- or bicyclic, optionally carrying substituents. Monocyclic heteroaryl includes 5 or 6 membered heteroaryl groups containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, sulfur and oxygen. Bicyclic heteroaryl includes 9 or  
30 10 membered fused-ring heteroaryl groups. Examples of heteroaryl include pyrrolyl, thienyl, furyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and benzo or pyridazo fused derivatives of such monocyclic heteroaryl groups, such as indolyl, benzimidazolyl, benzofuryl, quinolinyl, isoquinolinyl, quinazolinyl, pyrrolopyridine,  
35 imidazopyridine, or purinyl, all optionally substituted. Preferably, heteroaryl is pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, oxadiazolyl, triazolyl, oxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, indolyl, pyrrolopyridine or

imidazopyridine; in particular thiadiazolyl. Substituents considered are those mentioned above as substituents for phenyl, in particular lower alkyl, halo-lower alkyl, lower alkoxy-lower alkyl, hydroxy, lower alkoxy, halo-lower alkoxy, lower alkoxy-lower alkoxy, phenoxy, hydroxyphenoxy, halophenoxy, phenyl, halophenyl, hydroxyphenyl, halo, cyano or nitro, in  
5 particular lower alkyl, halo-lower alkyl, lower alkoxy, phenoxy, halophenoxy, phenyl, halophenyl, hydroxyphenyl, or halo.

Halo-lower alkyl is preferably fluoro-lower alkyl, especially trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl.

10

Halogen is fluorine, chlorine, bromine, or iodine, in particular fluorine and chlorine.

Lower alkoxy is especially methoxy, ethoxy, isopropoxy, or tert-butyloxy. Halo-lower alkoxy is preferably fluoro-lower alkoxy, especially difluoromethoxy.

15

Phenyl-lower alkyl includes phenyl and lower alkyl as defined hereinbefore, and is e.g. benzyl, 1-phenethyl, 2-phenethyl, or 3-phenylpropyl.

Heteroaryl-lower alkyl includes heteroaryl and lower alkyl as defined hereinbefore, and is  
20 e.g. 2-, 3- or 4-pyridylmethyl, 1- or 2-pyrrolylmethyl, 1-pyrazolylmethyl, 1-imidazolylmethyl, 2-(1-imidazolyl)ethyl or 3-(1-imidazolyl)propyl.

Optionally substituted lower alkylcarbonylamino is especially methyl- or ethyl-carbonylamino, methoxymethylcarbonylamino, halomethylcarbonylamino, cyanomethylcarbonyl-  
25 amino, or tert-butylaminomethylcarbonylamino.

Salts are especially the pharmaceutically acceptable salts.

Particular salts considered are those replacing hydrogen in a carboxylic acid function.  
30 Suitable cations are, e.g., sodium, potassium, calcium, magnesium or ammonium cations, or also cations derived by protonation from primary, secondary or tertiary amines containing, for example, lower alkyl, hydroxy-lower alkyl or hydroxy-lower alkoxy-lower alkyl groups, e.g., 2-hydroxyethylammonium, 2-(2-hydroxyethoxy)ethyldimethyl-  
ammonium, diethylammonium, di(2-hydroxyethyl)ammonium, trimethylammonium,  
35 triethylammonium, 2-hydroxyethyldimethylammonium, or di(2-hydroxyethyl)methyl-  
ammonium, also from correspondingly substituted cyclic secondary and tertiary amines, e.g., N-methylpyrrolidinium, N-methylpiperidinium, N-methylmorpholinium, N-2-hydroxy-



ethylpyrrolidinium, N-2-hydroxyethylpiperidinium, or N-2-hydroxyethylmorpholinium, and the like.

If the compounds contain a basic nitrogen atom, salts are especially pharmaceutically acceptable acid addition salts of such basic compounds. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2-, 3- or 4-methyl-benzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula (1), (2), (3) and (4) have valuable pharmacological properties. The invention also relates to these compounds and salts as defined hereinbefore for use as medicaments in combination with tetracyclines. A compound according to the invention shows prophylactic and therapeutic efficacy in combination with tetracyclines especially against bacterial infections caused by Gram-positive and Gram-negative pathogens with particular efficacy in tetracycline resistant bacterial strains. These compounds specifically bind to TetR and therefore prevent the transcriptional activation of tet resistance genes.

The compounds have a potentiating effect on the activity of tetracycline and other antibiotics of the tetracycline family, such as minocycline, doxycycline and tigecycline, in the treatment of tetracycline susceptible, intermediate and tetracycline resistant pathogens.

5

Particularly preferred is the use of a compound of formula (1), (2), (3) or (4) or a salt thereof according to the invention as a medicament in combination with tetracyclines for the prevention and treatment of tetracycline susceptible, intermediate and, in particular, tetracycline resistant bacterial infections caused by Gram-positive and Gram-negative

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bacterial pathogens. Such pathogens are Gram-positive pathogens such as

*Actinobacteria*, *Actinomyces*, *Actinomyces israelii*, *Bacillales*, *Bacillus*, *Clostridium*, *Clostridium acetobutylicum*, *Clostridium aerotolerans*, *Clostridium argentinense*, *Clostridium baratii*, *Clostridium beijerinckii*, *Clostridium bifementans*, *Clostridium botulinum*, *Clostridium butyricum*, *Clostridium cadaveris*, *Clostridium cellulolyticum*,

15

*Clostridium chauvoei*, *Clostridium clostridioforme*, *Clostridium colicanis*, *Clostridium difficile*, *Clostridium estertheticum*, *Clostridium fallax*, *Clostridium formicaceticum*, *Clostridium histolyticum*, *Clostridium innocuum*, *Clostridium kluyveri*, *Clostridium ljungdahlii*, *Clostridium novyi*, *Clostridium paraputrificum*, *Clostridium perfringens*, *Clostridium phytofermentans*, *Clostridium piliforme*, *Clostridium ragsdalei*, *Clostridium ramosum*, *Clostridium scatologenes*, *Clostridium septicum*, *Clostridium sordellii*,

20

*Clostridium sporogenes*, *Clostridium sticklandii*, *Clostridium tertium*, *Clostridium tetani*, *Clostridium thermosaccharolyticum*, *Clostridium tyrobutyricum*, *Corynebacterium*, *Corynebacterium bovis*, *Corynebacterium diphtheriae*, *Corynebacterium granulosum*, *Corynebacterium jeikeium*, *Corynebacterium minutissimum*, *Corynebacterium renale*,

25

*Enterococcus faecalis*, *Enterococcus faecium*, *Lactobacillales*, *Listeria*, *Nocardia asteroides*, *Nocardia brasiliensis*, *Nocardia farcinica*, *Propionibacterium acnes*, *Rhodococcus equi*, *Sarcina* (genus), *Solobacterium moorei*, *Staphylococcus aureus*, *Staphylococcus capitis*, *Staphylococcus caprae*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*,

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*Staphylococcus muscae*, *Staphylococcus nepalensis*, *Staphylococcus pettenkoferi*, *Staphylococcus saprophyticus*, *Staphylococcus succinus*, *Staphylococcus warneri*, *Staphylococcus xylosus*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus bovis*, *Streptococcus canis*, *Streptococcus iniae*, *Streptococcus lactarius*, *Streptococcus mitis*, *Streptococcus mutans*, *Streptococcus oralis*, *Streptococcus*

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*parasanguinis*, *Streptococcus peroris*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus rattii*, *Streptococcus salivarius*, *Streptococcus sanguinis*, *Streptococcus sobrinus*, *Streptococcus suis*, *Streptococcus salivarius* subsp.

*thermophilus*, *Streptococcus uberis*, *Streptococcus vestibularis*, and *Streptococcus viridians*, and Gram-negative pathogens such as *Acetobacter aceti*, *Acetobacter xylinum*, *Acinetobacter baumannii*, *Magnetospirillum magnetotacticum*, *Helicobacter pylori*, *Chromatium okenii*, *Thiocapsa literalis*, *Thiocapsa purpurea*, *Rhodobacter sphaeroides*,  
5 *Rhodospirillum rubrum*, *Rhodocyclus tenuis*, *Methylococcus capsulatus*, *Methylobacter albus*, *Methylomonas methanica*, *Aliivibrio fischeri*, *Photobacterium phosphoreum*, *Vibrio harveyi*, *Photococcus caeruleum*, *Nitrosomonas europaea*, *Nitrobacter vulgaris*, *Nitrobacter hamburgensis*, *Nitrococcus mobilis*, *E. coli*, *Salmonella typhimurium*, *Shigella dysenteriae*, *Yersinia pestis*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Vibrio*  
10 *cholerae*, *Neisseria gonorrhoeae*, *Acinetobacter baumannii*, *Moraxella bovis*, *Pseudomonas aeruginosa*, *Azotobacter vinelandii*, and *Rickettsia rickettsia*.

Of particular interest is the treatment of infections caused by tetracycline susceptible and in particular tetracycline resistant pathogens of the ESKAPE group of clinically relevant  
15 pathogens, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus sanguinis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Clostridium difficile*, *Acinetobacter baumannii*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Regarding the current medical use of tetracyclines in  
20 human and veterinary therapies the combination of compounds of formula (1), (2), (3) or (4) with tetracyclines in the treatment of infections of the urinary tract, the intestines and with chlamydia, especially in patients allergic to  $\beta$ -lactams and macrolides is of high relevance due to widespread development of resistance in the causative organisms. Additionally the use in the treatment of moderately severe acne and rosacea is  
25 considered, together with tetracycline, oxytetracycline, doxycycline, or minocycline.

Doxycycline in combination with compounds of formula (1), (2), (3) or (4) is also used as a prophylactic treatment for infection by *Bacillus anthracis* (anthrax) and is effective against *Yersinia pestis*, the infectious agent of bubonic plague. It can also be used for malaria  
30 treatment and prophylaxis, as well as for treating elephantiasis. Tetracyclines in combination with compounds of formula (1), (2), (3) or (4) are the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and *L. venereum* infection), *Rickettsia* (typhus, Rocky Mountain spotted fever), brucellosis, and spirochetal infections (borreliosis, syphilis, and Lyme disease). In addition, they may be  
35 used to treat anthrax, plague, tularemia, and Legionnaires' disease.

A compound of formula (1), (2), (3) or (4) is administered in combination with one or more tetracyclines, the combination therapy taking the form of fixed combinations, or the administration of a compound of the invention and one or more tetracyclines being staggered or given independently of one another.

5

Therapeutic agents selected from tetracyclines for possible combination are especially tetracycline, oxytetracycline, chlorotetracycline, demeclocycline, meclocycline, rolitetracycline, 6-thiatetracycline, 4-epi-anhydrochlortetracycline, aminomethylcycline, azatetracycline, fluorocycline, pentacycline, minocycline, doxycycline and glycylcyclines,  
10 in particular tigecycline.

With the groups of preferred compounds of formula (1), (2), (3) or (4) mentioned hereinafter, definitions of substituents from the general definitions mentioned hereinbefore may reasonably be used, for example, to replace more general definitions with more  
15 specific definitions or especially with definitions characterized as being preferred.

In particular, the invention refers to compounds *per se* and to a pharmaceutical compositions comprising such compounds of formula (1), (2), (3) and (4), wherein  
R<sup>1</sup> is hydrogen or methyl;  
20 R<sup>2</sup> is hydrogen or methyl;  
R<sup>3</sup> and R<sup>4</sup> are, independently of each other, hydrogen, lower alkyl, preferably n-butyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl, or methyl; halo-lower alkyl, preferably fluoro-lower alkyl, especially trifluoromethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; halogen, preferably fluorine, chlorine or bromine; cyano, lower alkoxy, preferably methoxy, ethoxy,  
25 isopropoxy, or tert-butyloxy; halo-lower alkoxy, preferably difluoromethoxy; optionally substituted lower alkylcarbonylamino, preferably methoxymethylcarbonylamino, cyanomethylcarbonylamino, tert-butylaminomethylcarbonylamino; or phenyl;  
R<sup>5</sup> is hydrogen, methyl, trifluoromethyl, fluorine, chlorine or cyano;  
R<sup>6</sup> is hydrogen, phenoxy or phenyl;  
30 R<sup>7</sup> is lower alkyl, cyclohexyl-lower alkyl, preferably cyclohexylmethyl or cyclohexylethyl; phenyl, unsubstituted or substituted by one, two or three substituents selected from lower alkyl, preferably n-butyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl, or methyl; halo-lower alkyl, preferably fluoro-lower alkyl, especially trifluoromethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; halogen, preferably fluorine, chlorine or bromine; cyano, hydroxy, lower  
35 alkoxy, preferably methoxy, ethoxy, isopropoxy, or tert-butyloxy; halo-lower alkoxy, preferably difluoromethoxy; phenoxy, halophenoxy, or phenyl; phenyl-lower alkyl, preferably phenylmethyl, 2-phenylethyl or 3-phenylpropyl, wherein phenyl is unsubstituted

- or substituted by one, two or three substituents selected from lower alkyl, preferably n-butyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl, or methyl; halo-lower alkyl, preferably fluoro-lower alkyl, especially trifluoromethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; halogen, preferably fluorine, chlorine or bromine; cyano, hydroxy, lower alkoxy, preferably
- 5 methoxy, ethoxy, isopropoxy, or tert-butyloxy; halo-lower alkoxy, preferably difluoromethoxy; phenoxy, halophenoxy, or phenyl; or thiadiazolyl substituted by phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl;
- $R^8$  is hydrogen, methyl, phenyl or halophenyl;
- A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the
- 10 A ring connection, or absent;
- X is CH or N;
- $R^9$  is hydrogen or methyl, if X is CH; or  $R^2$  and  $R^9$  together represent ethylene, if X is N;
- n is 1, 2, 3 or 4;
- m is 0 or 1; and
- 15 p is 0 or 1.

The invention preferably relates to such pharmaceutical compositions comprising a compound of formula (1) wherein n is 3 or 4, and to such compounds of formula (1) wherein n is 3 or 4 *per se*.

20

- Furthermore, the invention refers preferably to pharmaceutical compositions comprising compounds of formula (1), wherein
- $R^1$  is hydrogen;
- $R^2$  is hydrogen or methyl;
- 25  $R^3$  and  $R^4$  are, independently of each other, hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;
- $R^5$  is hydrogen;
- 30  $R^6$  is hydrogen, phenoxy or phenyl; and
- n is 1, 2, 3 or 4;

- in particular to such compositions wherein  $R^3$  is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano,
- 35 methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;
- $R^4$  is fluoro or trifluoromethyl;

and to such compounds of formula (1) *per se* wherein R<sup>3</sup> is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, hydroxy, methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino; and  
5 R<sup>4</sup> is fluoro or trifluoromethyl.

More preferably, the invention refers to compounds *per se* and to a pharmaceutical composition comprising such compounds of formula (2), wherein  
10 R<sup>1</sup> is hydrogen;  
R<sup>2</sup> is hydrogen or methyl;  
R<sup>3</sup> and R<sup>4</sup> are, independently of each other, hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-  
15 butylaminomethylcarbonylamino;  
R<sup>5</sup> is hydrogen; and  
R<sup>6</sup> is hydrogen, phenoxy or phenyl;  
X is CH or N;  
R<sup>9</sup> is hydrogen or methyl, if X is CH; or R<sup>2</sup> and R<sup>9</sup> together represent ethylene, if X is N;  
20 and  
n is 2, 3 or 4, if X is CH; or n is 2, if X is N;

in particular to such compositions and compounds *per se* wherein X is N and n is 2.

25 Likewise, the invention refers preferably to compounds *per se* and to a pharmaceutical composition comprising such compounds of formula (3), wherein  
R<sup>1</sup> is hydrogen;  
R<sup>2</sup> is hydrogen or methyl;  
R<sup>6</sup> is hydrogen, phenoxy or phenyl;  
30 R<sup>7</sup> is lower alkyl or phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by lower alkyl, halo-lower alkyl, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl;  
R<sup>8</sup> is hydrogen, methyl, phenyl or halophenyl;  
m is 0 or 1; and  
p is 0 or 1;  
35  
in particular to such compositions and compounds wherein p is 0.

Likewise, the invention refers preferably to compounds *per se* and to a pharmaceutical composition comprising such compounds of formula (4), wherein

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is hydrogen or methyl;

- 5 R<sup>7</sup> is lower alkyl, preferably n-butyl, sec-butyl, tert-butyl, n-propyl, isopropyl, ethyl or methyl, cyclohexyl-lower alkyl, preferably cyclohexylmethyl or cyclohexylethyl; phenyl, unsubstituted or substituted by one or two substituents selected from lower alkyl, preferably ethyl or methyl; halo-lower alkyl, preferably fluoro-lower alkyl, especially trifluoromethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; halogen, preferably fluorine or
- 10 chlorine; hydroxy, lower alkoxy, preferably methoxy or ethoxy; phenoxy, halophenoxy, preferably fluorophenoxy or chlorophenoxy; or phenyl; phenyl-lower alkyl, preferably phenylmethyl, 2-phenylethyl or 3-phenylpropyl, wherein phenyl is unsubstituted or substituted by one or two substituents selected from lower alkyl, preferably ethyl or methyl; halo-lower alkyl, preferably fluoro-lower alkyl, especially trifluoromethyl, 2,2,2-
- 15 trifluoroethyl, or pentafluoroethyl; halogen, preferably fluorine or chlorine; hydroxy, lower alkoxy, preferably methoxy or ethoxy; phenoxy, halophenoxy, preferably fluorophenoxy or chlorophenoxy, or phenyl; or thiadiazolyl substituted by phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl; and
- A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the
- 20 A ring connection, or absent.

Most preferred are the compounds of the examples.

- A compound of the invention may be prepared by processes that, though not applied
- 25 hitherto for the new compounds of the present invention, are known *per se*, in particular processes as described in the Examples. If so desired, an obtainable compound of formula (1), (2), (3) or (4) is converted into another compound of formula (1), (2), (3) or (4), a free compound of formula (1), (2), (3) or (4) is converted into a salt, an obtainable salt of a compound of formula (1), (2), (3) or (4) is converted into the free compound or
- 30 another salt, and/or a mixture of isomeric compounds of formula (1), (2), (3) or (4) is separated into the individual isomers.

- In the mentioned processes, protecting groups may be used. The protecting groups may already be present in precursors and should protect the functional groups concerned
- 35 against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal,

typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned.

5

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference books for peptide synthesis and in special books on protective groups such as T.W. Greene & P.G.M. Wuts, "Protective Groups in Organic Synthesis", Wiley, 3<sup>rd</sup> edition 1999.

10

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

15

In the conversion of an obtainable compound of formula (1), (2), (3) or (4) into another compound of formula (1), (2), (3) or (4), an amino group may be alkylated or acylated to give the correspondingly substituted compounds. Alkylation may be performed with an alkyl halide or an activated alkyl ester. For methylation, diazomethane may be used. Alkylation may also be performed with an aldehyde under reducing conditions. For acylation the corresponding acyl chloride is preferred. Alternatively, an acid anhydride may be used, or acylation may be accomplished with the free acid under conditions used for amide formation known *per se* in peptide chemistry, e.g. with activating agents for the carboxy group, such as 1-hydroxybenzotriazole, optionally in the presence of suitable catalysts or co-reagents. Furthermore amine may be transformed into heteroaryl and heterocyclyl under reaction conditions typical for such cyclizations.

20

25

A hydroxy group may be alkylated (etherified) or acylated (esterified) to give the correspondingly substituted compounds in a procedure related to the one described for an amino group. Alkylation may be performed with an alkyl halide or an activated alkyl ester. For methylation, diazomethane may be used. For acylation the corresponding acyl chloride or acid anhydride may be used, or acylation may be accomplished with the free acid and a suitable activating agent.

35

Reduction of a nitro group in a nitro-substituted aryl or heteroaryl group to give the corresponding amino group is done, e.g., with iron powder in alcohol or with other



reducing agents.

A carboxy group in a carboxy-substituted aryl or heteroaryl group may be amidated under conditions used for amide formation known *per se* in peptide chemistry, e.g. with the  
5 corresponding amine and an activating agent for the carboxy group, such as 1-hydroxy-benzotriazole, optionally in the presence of suitable catalysts or co-reagents.

A chloro, bromo or iodo substituent in an aryl or heteroaryl group may be replaced by phenyl or a phenyl derivative by reaction with a suitable phenylboronic acid in a Suzuki  
10 reaction as described above.

Salts of a compound of formula (1), (2), (3) or (4) may be prepared in a manner known *per se*, e.g. by treatment with an inorganic or organic base, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically  
15 potassium carbonate or sodium hydroxide.

Salts can usually be converted to free compounds, e.g. by treating with suitable acids.

It should be emphasized that reactions analogous to the conversions mentioned in this  
20 chapter may also take place at the level of appropriate intermediates.

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to  
25 dissolve these, in the absence or presence of catalysts, condensing agents or neutralising agents, for example ion exchangers, typically cation exchangers, for example in the H<sup>+</sup> form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at -80 to +60°C, at -20 to +40°C, at room temperature,  
30 or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may also be present during the reaction of such compounds,  
35 provided the reaction is not thereby disturbed.

At all reaction stages, isomeric mixtures that occur can be separated into their individual isomers, e.g. diastereomers or enantiomers, or into any mixtures of isomers, e.g. racemates or diastereomeric mixtures.

- 5 The invention relates also to those forms of the process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and
- 10 further processes the said compound *in situ*. In the preferred embodiment, one starts from those starting materials which lead to the compounds described hereinabove as preferred, particularly as especially preferred, primarily preferred, and/or preferred above all.

- In the preferred embodiment, a compound of formula (1), (2), (3) or (4) is prepared
- 15 according to or in analogy to the processes and process steps defined in the Examples.

- The compounds of formula (1), (2), (3) or (4), including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization, i.e. be present as solvates.

20

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

25

Starting materials are known, commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

- The present invention relates also to pharmaceutical compositions that comprise a
- 30 compound of formula (1), (2), (3) or (4) as active ingredient and that can be used in combination with tetracyclines in the treatment of infective diseases mentioned at the beginning. Compositions for enteral administration, such as nasal, buccal, rectal, uretal or, especially, oral administration to warm-blooded animals, especially humans, are preferred. The compositions comprise the active ingredient alone or, preferably, together
- 35 with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends upon the tetracycline used, the disease to be treated and upon the species, its age,

weight, and individual condition, the individual pharmacokinetic data, and the mode of administration.

The present invention relates especially to pharmaceutical compositions that comprise a  
5 compound of formula (1), (2), (3) or (4), a tautomer or a pharmaceutically acceptable salt, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable carrier.

The invention relates also to pharmaceutical compositions for use in combination with tetracyclines in a method for the prophylactic or especially therapeutic management of the  
10 human or animal body, in particular in a method of treating infective disease, especially those mentioned hereinabove.

The invention relates also to processes and to the use of compounds of formula (1), (2), (3) or (4) for the preparation of pharmaceutical preparations which comprise compounds  
15 of formula (1), (2), (3) or (4) as active component (active ingredient).

A pharmaceutical composition for the prophylactic or especially therapeutic management of an infective disease, of a warm-blooded animal, especially a human, comprising a novel compound of formula (1), (2), (3) or (4) as active ingredient in combination with a  
20 tetracycline in a quantity that is prophylactically or especially therapeutically active against the said infectious diseases, is likewise preferred. Preferred are pharmaceutical compositions suitable for oral administration.

The pharmaceutical compositions comprise from approximately 1% to approximately  
25 95% active ingredient, single-dose administration forms comprising in the preferred embodiment from approximately 20% to approximately 90% active ingredient and forms that are not of single-dose type comprising in the preferred embodiment from

In *in vitro* tests, the compounds of formula (1), (2), (3) or (4) show specific activity in i)  
30 TetR/tetO interaction and binding experiments and in ii) microdilution assays with clinical patient isolates that are resistant to tetracyclines where combinations of compounds of formula (1), (2), (3) or (4) significantly reduce the MIC of tetracyclines (Table Experimental part).

35 Pharmaceutical compositions according to the invention are compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as intravenous, intramuscular or subcutaneous

administration. The compositions comprise the compound of formula (1), (2), (3) or (4) alone or mixed with the tetracycline, and preferably together with a pharmaceutically acceptable carrier. The dosage of the active ingredients depends upon the tetracycline used, the patient, its age, weight, and individual condition, the individual pharmacokinetic data, and the mode of administration.

The pharmaceutical compositions comprise from approximately 5% to approximately 95% of active ingredient(s). Single-dose administration forms comprise from approximately 20% to approximately 90% of the mentioned compound of formula (1), (2), (3) or (4), optionally in a mixture together with a tetracycline, and forms that are not of single-dose type from approximately 5% to approximately 20% of the mentioned compound or compound mixture. Unit dose forms are, for example, coated and uncoated tablets, ampoules, vials, suppositories, or capsules. Further dosage forms are, for example, ointments, creams, pastes, foams, tinctures, lip-sticks, drops, syrups, sprays, and the like. Examples are capsules containing from about 0.05 g to about 1.0 g of a mixture of the active ingredients.

It is possible to use the mixture of a compound of formula (1), (2), (3) or (4) with a tetracycline in two separate pharmaceutical unit dose forms, and such a combination is also part of the present invention.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, coating, dissolving, emulsifying or lyophilizing processes. Optionally, the compounds can be formulated in liposomes.

For parenteral administration solutions of the active ingredients are preferred, and also suspensions, emulsions or dispersions, especially isotonic aqueous solutions, dispersions, emulsions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredients alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethyl-

cellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80<sup>®</sup> (polyoxyethylene(20)sorbitan mono-oleate).

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semi-  
5 synthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, especially glycol and glycerol. As  
10 mixtures of fatty acid esters, vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and groundnut oil are especially useful.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

15 Suitable carriers for oral compositions are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose,  
20 hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium  
25 stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable  
30 organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

35 Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as

glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved, emulsified or suspended in suitable liquid  
5 excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example,  
10 suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

The present invention relates furthermore to a method for the treatment of bacterial  
15 infections, which comprises administering a compound of formula ((1), (2), (3) or (4) as defined hereinabove, and of a mixture of a compound of formula (1), (2), (3) or (4), and of tetracycline or of another member of the tetracycline family of antibiotics, such as minocycline, doxycycline and tigecycline, in a quantity effective against said disease, to a warm-blooded animal requiring such treatment. The mixture can be administered in the  
20 form of pharmaceutical compositions comprising the mixture, or also the components separately at the same time or at different times within the day, prophylactically or therapeutically, preferably in an amount effective against the specific disease, to a warm-blooded animal, for example a human, requiring such treatment. In the case of an individual having a bodyweight of about 70 kg the daily dose of the mixture administered  
25 is from approximately 0.5 g to approximately 5 g, preferably from approximately 0.05 g to approximately 2 g, of a mixture comprising from 5% to approximately 95% containing the components in relative amounts of between 1:1 up to 1:10'000, preferably 1:10 up to 1:5'000.

30 The following Examples serve to illustrate the invention without limiting the invention in its scope.

## Examples

### Liquid chromatography (LC)

HPLC Column: Reverse Phase, Uptisphere Strategy C18-2, 5  $\mu$ m 4.6x250 mm;

- 5 Wavelength: 254 nm or 280 nm; HPLC Apparatus Type: *Agilent 1100 Series*, DAD detector; MS Apparatus Type: *Agilent MSD Trap XCT* positive/negative mode switching, Ionization mode APCI.

### LCMS System 01 (LCMS 01): Gradient 01

Solvent A: Water/methanol (95:5), 0.2% acetic acid; Solvent B: Methanol/water (95:5),

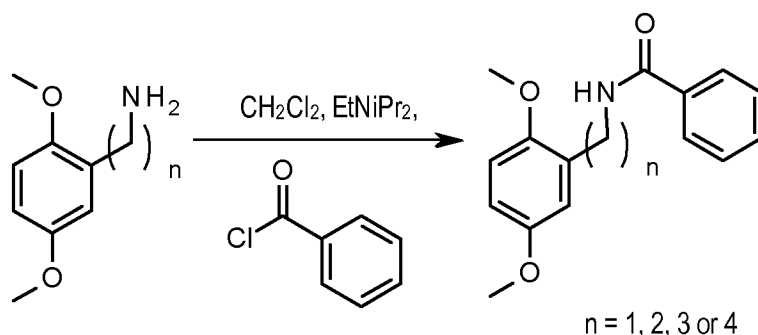
- 10 0.2% acetic acid;

Time(min)	Flow(mL/min)	%A	%B
0.00	1	100	0
10.00	1	0	100
18.00	1	0	100
18.10	1	100	0
20.00	1	100	0

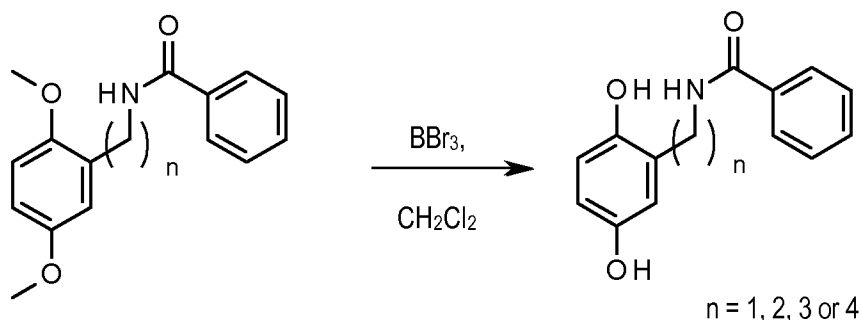
Examples 1 – 3, 5 – 11 and 39 – 42, compounds of formula (1)

General synthesis scheme for compounds of formula (1)

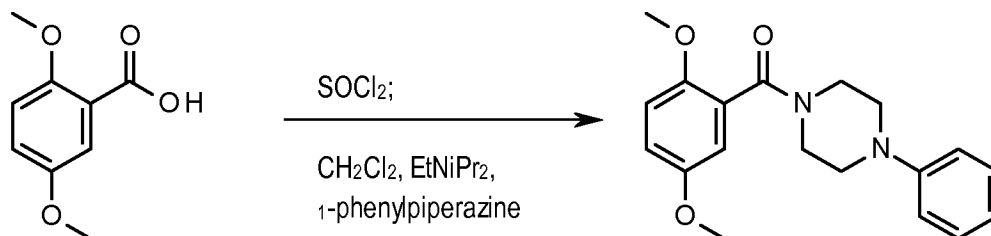
- 15 Step 1



- To a magnetically stirred solution of 2,5-dimethoxybenzylamine ( $n = 1$ ) (500 mg, 2.99 mmol, 0.45 mL) in  $\text{CH}_2\text{Cl}_2$  (4 mL) at room temperature was added drop wise benzoyl chloride (504 mg, 3.59 mmol, 0.42 mL) followed by ethyldiisopropylamine (0.5 mL). The mixture was stirred for a further 22.5 hours before being concentrated *in vacuo*. The residue was purified over silica gel with 0-50% ethyl acetate in cyclohexane to yield
- 20 N-[(2,5-dimethoxyphenyl)methyl]benzamide ( $n = 1$ ) (728 mg, 2.68 mmol) in 90% yield.

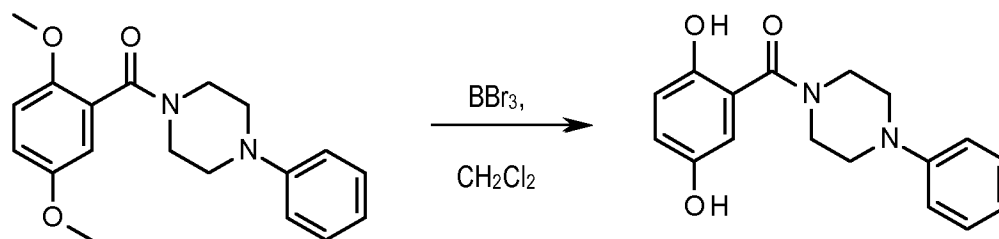
Step 2

To a magnetically stirred solution of N-[(2,5-dimethoxyphenyl)methyl]benzamide ( $n = 1$ ) (563 mg, 2.08 mmol) in  $\text{CH}_2\text{Cl}_2$  at room temperature was added drop wise boron tribromide (2.08 g, 8.30 mmol, 0.80 mL) and stirred for a further 21 hours before being quenched cautiously with MeOH (4 mL). The reaction mixture was then concentrated *in vacuo* and further portions of MeOH (5 x 4 mL) were added and concentrated in sequence. The residue was purified over silica gel with 0-100% EtOAc in cyclohexane to yield N-[(2,5-dihydroxyphenyl)methyl]benzamide ( $n = 1$ , Example 1) (450 mg, 1.85 mmol) in 89% yield. LCMS  $\text{ESI}^+$ : 244.0 ( $\text{M}+\text{H}^+$ ),  $R_t$  7.5 min (LCMS 01).

General synthesis scheme for compounds of formula (2)Synthetic scheme for Example 4, 43 and 44Step 1

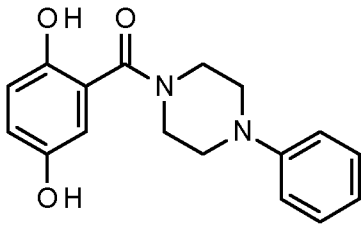
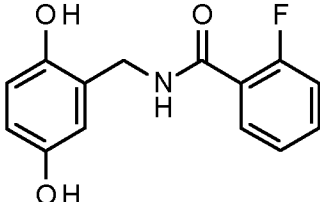
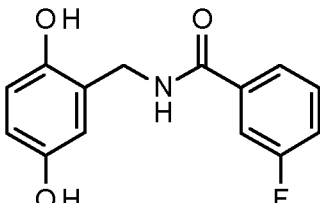
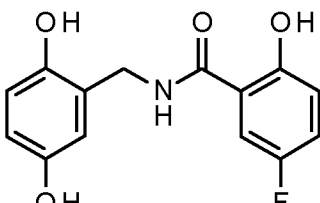
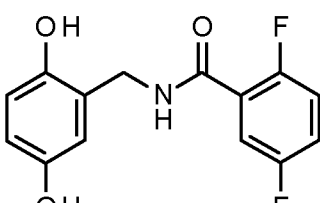
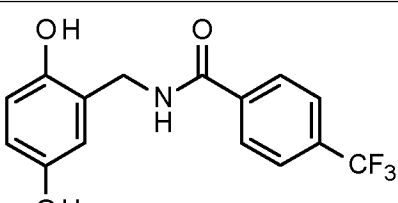
A solution of 2,5-dimethoxybenzoic acid (100 mg, 0.549 mmol) in  $\text{SOCl}_2$  (1 mL) at  $75^\circ\text{C}$  was stirred magnetically for 1 h, then cooled and concentrated *in vacuo* to remove excess thionylchloride. To a mixture of this acid chloride in 1 mL  $\text{CH}_2\text{Cl}_2$  was added drop wise 1-phenylpiperazine (89 mg, 0.549 mmol, 120  $\mu\text{L}$ ) solution in 1 mL  $\text{CH}_2\text{Cl}_2$  followed by ethyldiisopropylamine (0.2 mL). The mixture was stirred for a further 18.5 hours before being concentrated *in vacuo*. The residue was purified over silica gel with 0-100% ethyl acetate in cyclohexane to yield (2,5-dimethoxyphenyl)-(4-phenylpiperazin-1-yl)methanone (170 mg, 0.521 mmol) in 95 % yield.

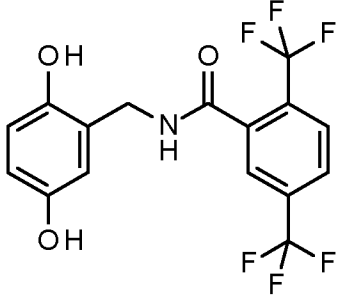
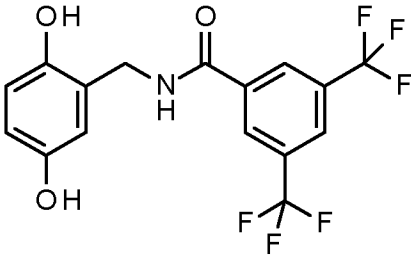
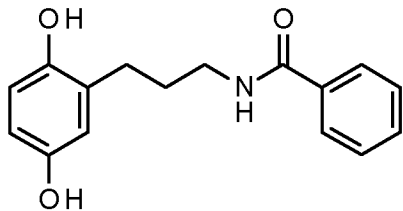
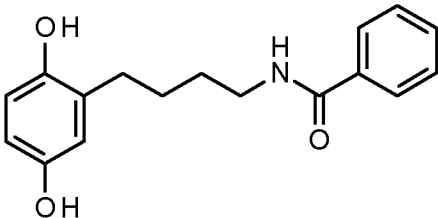
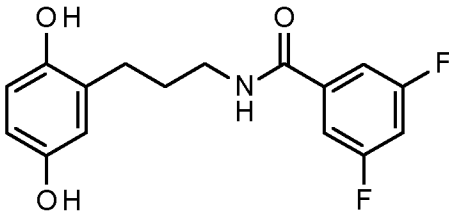
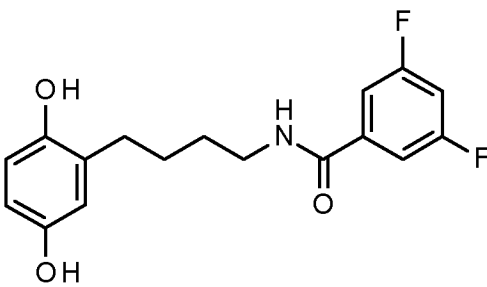


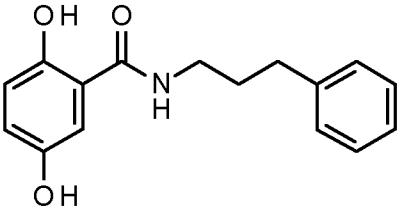
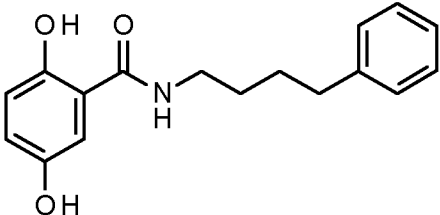
Step 2

To a magnetically stirred solution of (2,5-dimethoxyphenyl)-(4-phenylpiperazin-1-yl)-methanone (160 mg, 0.490 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) at 0°C was added drop wise boron tribromide (246 g, 0.980 mmol, 93 µL) and stirred at room temperature for a further 20 hours before being quenched cautiously with MeOH (4 mL). The reaction mixture was then concentrated *in vacuo* and further portions of MeOH (4 x 7 mL) were added and concentrated in sequence. The residue was purified over silica gel with 0-100% EtOAc in cyclohexane, and semi-preparative HPLC with 50 to 95% MeOH in H<sub>2</sub>O to yield N-[(2,5-dihydroxyphenyl)methyl]benzamide (15 mg, 0.050 mmol), Example 4, in 10% yield. LCMS ESI<sup>+</sup>: 299 [M+H]<sup>+</sup>, ESI<sup>-</sup>: 297 [M-H]<sup>-</sup>, R<sub>t</sub> 11.0 min (LCMS 01).

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
1		243.09	7.5	244 [M+H] <sup>+</sup>
2		279.07	11.0	280 [M+H] <sup>+</sup>
3		257.11	9.9	258 [M+H] <sup>+</sup>

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
4		298.13	11.0	299 [M+H] <sup>+</sup> 297 [M-H] <sup>-</sup>
5		261.08	9.9	259 [M-H] <sup>-</sup>
6		261.08	10.4	260 [M-H] <sup>-</sup>
7		277.08	10.8	278 [M+H] <sup>+</sup> 276 [M-H] <sup>-</sup>
8		279.07	10.2	280 [M+H] <sup>+</sup> 278 [M-H] <sup>-</sup>
9		311.08	11.7	312 [M+H] <sup>+</sup> 310 [M-H] <sup>-</sup>

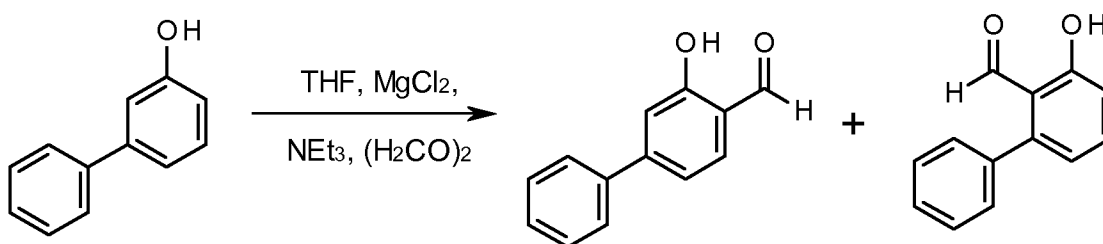
Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
10		379.06	11.4	380 [M+H] <sup>+</sup> 378 [M-H] <sup>-</sup>
11		379.06	12.7	380 [M+H] <sup>+</sup> 378 [M-H] <sup>-</sup>
39		271.12	10.34	272 [M+H] <sup>+</sup> 270 [M-H] <sup>-</sup>
40		285.14	10.45	286 [M+H] <sup>+</sup>
41		307.10	11.23	308 [M+H] <sup>+</sup> 306 [M-H] <sup>-</sup>
42		321.12	11.38	322 [M+H] <sup>+</sup> 320 [M-H] <sup>-</sup>

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
43		271.12	12.35	272 [M+H] <sup>+</sup> 270 [M-H] <sup>-</sup>
44		285.14	12.78	286 [M+H] <sup>+</sup> 284 [M-H] <sup>-</sup>

Examples 12, 13 and 17, compound of formula (3)

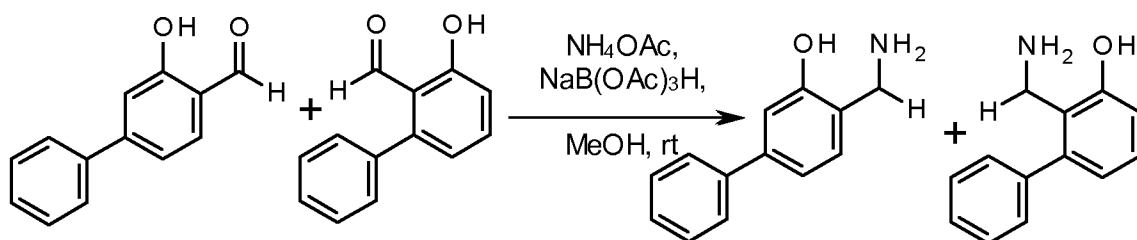
General synthesis scheme

Step 1

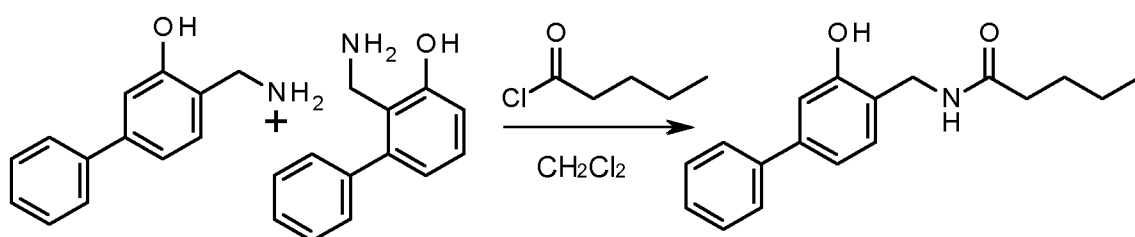


5

To a magnetically stirred solution of 3-phenylphenol (457 mg, 2.69 mmol) in tetrahydrofuran (30 mL) at room temperature was added magnesium chloride (511 mg, 5.37 mmol), triethylamine (543 mg, 5.37 mmol, 0.75 mL), and then paraformaldehyde (242 mg, 8.06 mmol). The reaction mixture was heated to 66°C and stirred for 4 days, cooled to room temperature and the solvents removed *in vacuo*. The residue was partitioned between H<sub>2</sub>O (50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (50 mL), and the layers shaken and separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL), and the combined organic extracts were washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified over silica gel with 0-30% ethyl acetate in cyclohexane to yield an approximate 1:1 inseparable mixture of 2-hydroxy-4-phenylbenzaldehyde and 2-hydroxy-6-phenylbenzaldehyde (300 mg, 1.51 mmol) in 56% yield.

Step 2

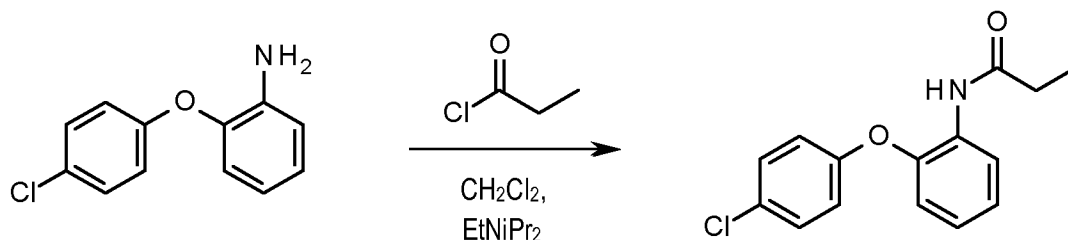
A solution of 2-hydroxy-4-phenylbenzaldehyde/2-hydroxy-6-phenylbenzaldehyde (300 mg, 1.51 mmol) and ammonium acetate (1.28 g, 16.65 mmol) in methanol (20 mL) was stirred magnetically at room temperature for 1 hour. To the mixture was added sodium triacetoxyborohydride (642 mg, 3.03 mmol) and stirred at room temperature for a further 18 hours. The reaction was quenched by slow addition of 1N aqueous hydrochloric acid and adjusted to pH 2. The mixture was concentrated *in vacuo*, and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and adjusted to pH 12 with 4N NaOH. The layers were shaken and separated, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 40 mL). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified over silica gel with 0-20% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield an approximate 1:1 inseparable mixture of 2-(aminomethyl)-3-phenylphenol and 2-(aminomethyl)-5-phenylphenol in 13% yield.

Step 3

To a magnetically stirred solution of 2-(aminomethyl)-3-phenylphenol/2-(aminomethyl)-5-phenylphenol (40 mg, 0.20 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at room temperature was added dropwise pentanoylchloride (29 mg, 0.24 mmol, 29  $\mu$ L) followed several minutes later by ethyldiisopropylamine (0.1 mL). The reaction was stirred at room temperature for a further 18.5 hours, quenched with H<sub>2</sub>O (10 mL) and partitioned with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified over silica gel with 0-30% ethyl acetate in cyclohexane to yield N-[(2-hydroxy-4-phenyl-phenyl)-methyl]pentanamide (13 mg, 0.05 mmol), Example 12, in 24% yield as the only isolated product. LCMS ESI<sup>+</sup>: 284 [M+H]<sup>+</sup>, R<sub>t</sub> 8.9 min (LCMS 01)

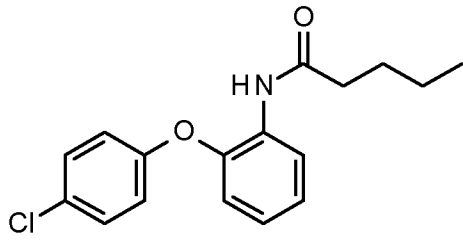
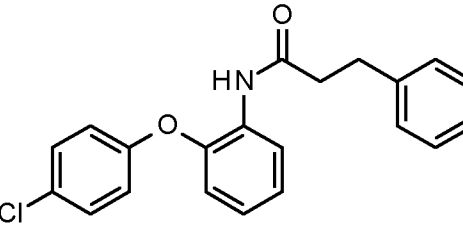
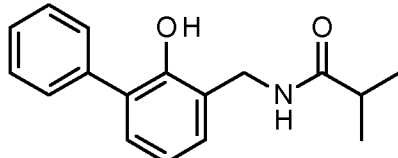
Examples 14 – 16, compound of formula (3)

General synthesis scheme



To a magnetically stirred solution of 2-(4-chlorophenoxy)aniline (95 mg, 0.432 mmol, 76  $\mu$ L) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) at room temperature was added dropwise propionylchloride (48 mg, 0.518 mmol, 45  $\mu$ L) followed several minutes later by ethyldiisopropylamine (0.2 mL). The reaction was stirred at room temperature for a further 17 hours, quenched with H<sub>2</sub>O (10 mL) and partitioned with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified over silica gel with 0-50% ethyl acetate in cyclohexane to yield N-[2-(4-chlorophenoxy)phenyl]propanamide (109 mg, 0.395 mmol), Example 14, in 91% yield. LCMS ESI<sup>+</sup>: 276 [M+H]<sup>+</sup>, R<sub>t</sub> 9.1 min (LCMS 01).

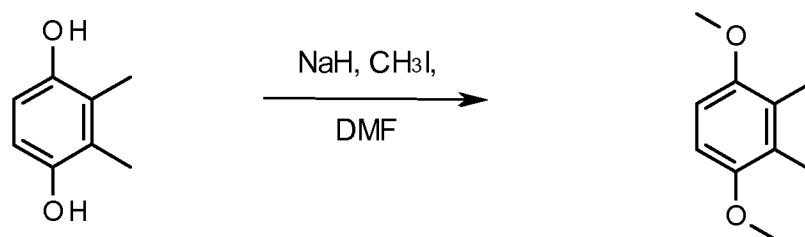
Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
12		283.16	8.9	284 [M+H] <sup>+</sup>
13		299.15	9.3	300 [M+H] <sup>+</sup>
14		275.07	9.1	276 [M+H] <sup>+</sup>

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
15		303.10	9.4	304 [M+H] <sup>+</sup>
16		351.10	9.5	352 [M+H] <sup>+</sup>
17		269.14	8.9	270 [M+H] <sup>+</sup>

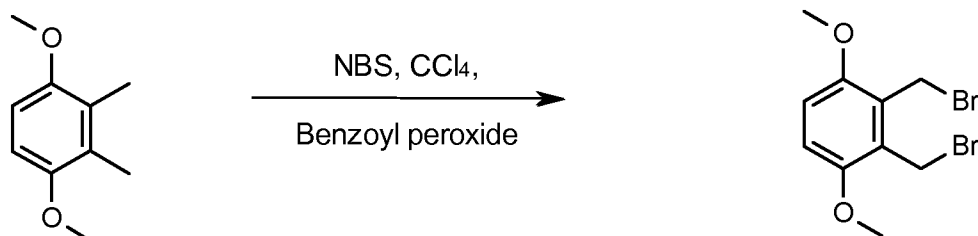
Examples 18 – 19, 21 – 38, compound of formula (4)

#### General synthesis scheme

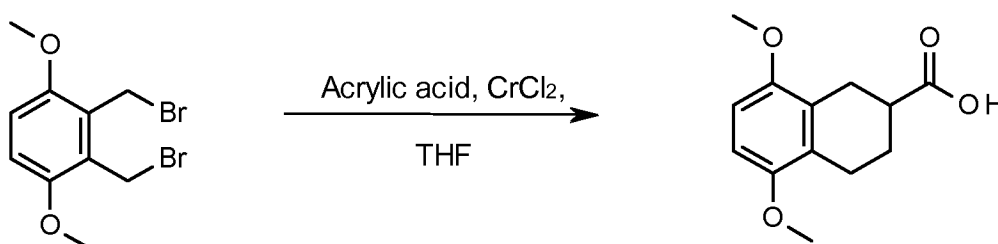
##### 5 Step 1



To a magnetically stirred solution of 2,3-dimethylhydroquinone (8.60 g, 62.3 mmol) in dry DMF (100 mL) at 0°C and protecting gas (argon) was added sodium hydride (10.26 g, 256 mmol) in one portion followed by methyl iodide (21.47 g, 151 mmol, 9.4 mL) over a period of 40 minutes at -5°C. The reaction was stirred for a further 3.5 hours before being quenched at 0°C with H<sub>2</sub>O (150 mL). The reaction mixture was stirred for further 20 minutes, and the precipitate was filtered off, washed with H<sub>2</sub>O and dried at 40°C *in vacuo*. The solid was dissolved in methanol (60 mL) at 70°C and cooled to room temperature while stirring, and the precipitation was filtered off, washed with cold methanol and dried to yield 1,4-dimethoxy-2,3-dimethylbenzene (9.86 g, 59.3 mmol) in 95% yield.

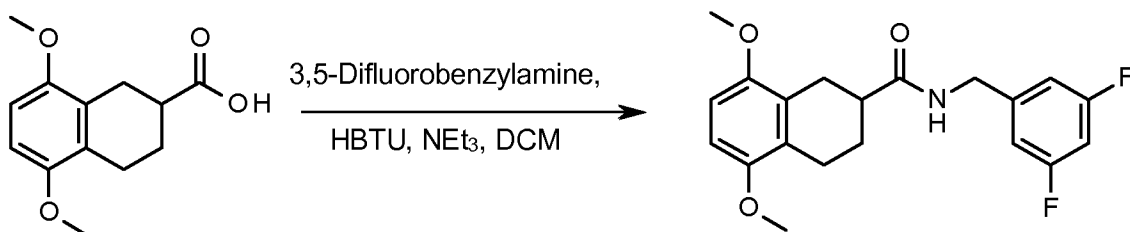
Step 2

To a magnetically stirred solution of 1,4-dimethoxy-2,3-dimethylbenzene (13.90 g, 83.6 mmol) in carbon tetrachloride (300 mL) at room temperature was added N-bromo-succinimide (32.2 g, 176 mmol) in one portion, and the reaction mixture was heated up to 65°C. Benzoyl peroxide (0.54 g, 2.23 mmol) was added at 65°C, and the reaction mixture stirred for further 4 hours before cooling down to 55°C. The reaction mixture was filtered, the solid washed with carbon tetrachloride, and the combined filtrates were concentrated *in vacuo* to yield 2,3-bis(bromomethyl)-1,4-dimethoxybenzene (26.8 g, 82.7 mmol) in 99% yield.

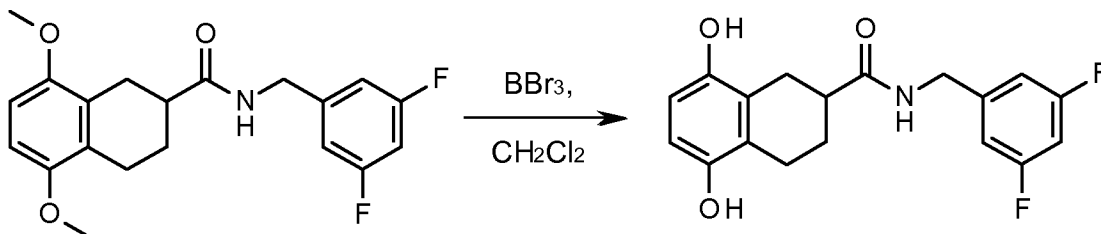
Step 3

To a magnetically stirred solution of 2,3-bis(bromomethyl)-1,4-dimethoxybenzene (26.8 g, 82.7 mmol) in tetrahydrofuran (500 mL) at room temperature was added acrylic acid (28.61 g, 397 mmol, 27.2 ml) in one portion, and the reaction mixture was cooled down to 0°C. Chromium(II) chloride was added in small portions over a period of 2 hours, and the reaction mixture was stirred for 15.5 hours at room temperature. The reaction mixture was concentrated *in vacuo* to 150 mL, filtered, and the filtrate was quenched with H<sub>2</sub>O (250 mL). The aqueous layer was extracted with ethyl acetate : cyclohexane 1:2, (3 x 250 mL), and the combined organic extracts were washed with brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was taken up in ethyl acetate (50 mL), and the precipitation was filtered off, washed with ethyl acetate until the filtrate was clear and colourless, and then dried *in vacuo* at 40°C to yield 5,8-dimethoxytetralin-2-carboxylic acid (6.46 g, 27.3 mmol) in 41% yield.

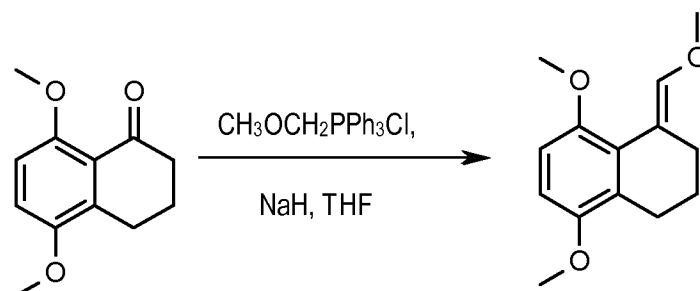


Step 4

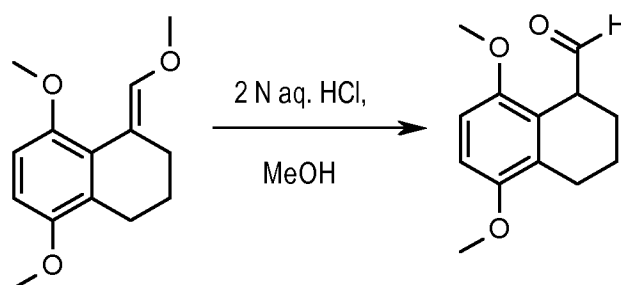
- A mixture of 5,8-dimethoxytetralin-2-carboxylic acid (2.00 g, 8.46 mmol), 3,5-difluorobenzylamine (0.74 g, 5.17 mmol, 1.8 mL), triethylamine (2.57 g, 25.4 mmol, 3.52 mL) and HBTU (3.53 g, 9.31 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (90 mL) was stirred magnetically at room temperature and under nitrogen atmosphere for 19 hours before being diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic phase was washed with 20% aq. K<sub>2</sub>CO<sub>3</sub> (3 x 80 mL), 10% aq. citric acid (80 mL), H<sub>2</sub>O (2 x 80 mL), brine (80 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (250 mL), washed with H<sub>2</sub>O (3 x 100 mL), brine (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to yield N-[(3,5-difluorophenyl)methyl]-5,8-dimethoxy-tetralin-2-carboxamide (2.95 g, 8.16 mmol) in 95% yield.

Step 5

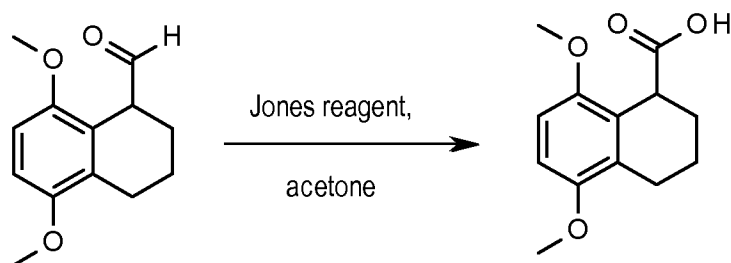
- To a magnetically stirred solution of N-[(3,5-difluorophenyl)methyl]-5,8-dimethoxy-tetralin-2-carboxamide (160 mg, 0.443 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at -10°C was added drop wise boron tribromide (221.8 mg, 0.885 mmol, 0.08 mL), and the mixture stirred for 15 minutes below -5°C and a further 17 hours at room temperature before being quenched cautiously at 0°C with MeOH (10 mL). The reaction mixture was then concentrated *in vacuo*, and further portions of MeOH (7 x 10 mL) were added and concentrated in sequence. The residue was dissolved in MeOH (2 mL), H<sub>2</sub>O (60 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 40 mL), the combined organic phases washed with H<sub>2</sub>O (40 mL), brine (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified over RP-C18 with 5-95% MeOH in H<sub>2</sub>O to yield N-[(3,5-difluorophenyl)methyl]-5,8-dihydroxy-tetralin-2-carboxamide (35 mg, 105.0 mmol), Example 23, in 24% yield. LCMS ESI<sup>+</sup>: 334 [M+H]<sup>+</sup>, 332 [M+H]<sup>-</sup>, R<sub>t</sub> 11.0 min (LCMS 01)

Synthetic scheme for example 20Step 1

To a magnetically stirred mixture of (methoxymethyl)triphenylphosphonium chloride (3.14 g, 9.07 mmol) in THF (100 mL) at room temperature was added NaH (490 mg, 12.36 mmol) and stirred at room temperature for 15 minutes. To the reaction was added 5,8-dimethoxytetralin-1-one (1.70 g, 8.24 mmol) in THF (40 mL) and stirred at room temperature for 30 minutes, then at reflux under nitrogen atmosphere for 15 hours, cooled to room temperature, and ethanol (80 mL) added. Aqueous ammonium chloride solution (80 mL) was added, the mixture extracted with ethyl acetate (3 x 80 mL), and the extracts washed with  $\text{H}_2\text{O}$  (2 x 60 mL), brine (70 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was purified over silica gel with 0-100% ethyl acetate in cyclohexane to yield 5,8-dimethoxytetralin-1-carbaldehyde (1.54 g, 6.57 mmol) in 80% yield.

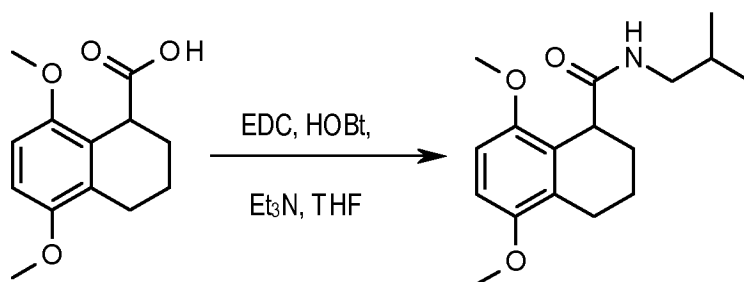
15 Step 2

To a magnetically stirred mixture of (1E)-5,8-dimethoxy-1-(methoxymethylene)tetralin (1.54 g, 6.57 mmol) in MeOH (15 mL) was added 2 N aq. HCl (77 mL) and stirred at reflux under nitrogen atmosphere for 15 hours, cooled to room temperature and MeOH removed *in vacuo*. The residue was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 100 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was purified over silica gel with 0-100% ethyl acetate in cyclohexane to yield 5,8-dimethoxytetralin-1-carbaldehyde (1.21 g, 5.49 mmol) in 84% yield.

Step 3

To a magnetically stirred mixture of 5,8-dimethoxytetralin-1-carbaldehyde (1.21 g, 5.49 mmol) in acetone (12 mL) at 0°C was added Jones reagent (1 mL) and stirred at room temperature under nitrogen atmosphere for 1 hour before being diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The solution was washed with 4% aq. NaOH (2 x 30 mL) and extracted with ethyl acetate (50 mL). The aqueous phase was acidified with 2 N HCl, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL), washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to yield 5,8-dimethoxytetralin-1-carboxylic acid (250 mg, 1.06 mmol) in 19% yield.

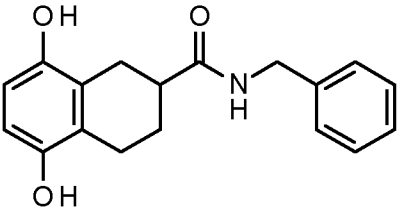
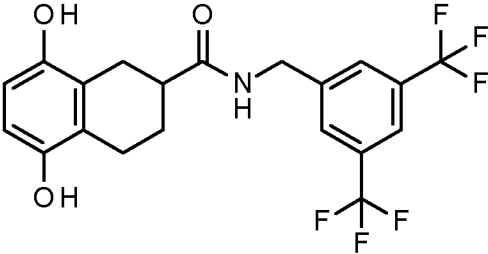
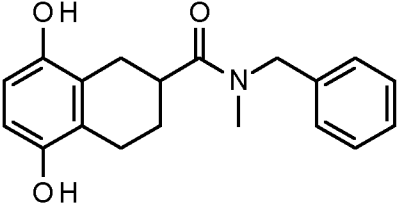
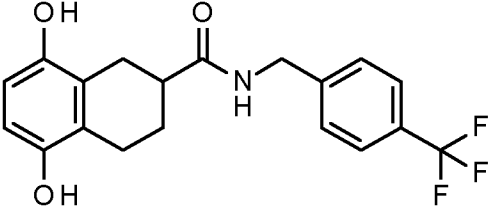
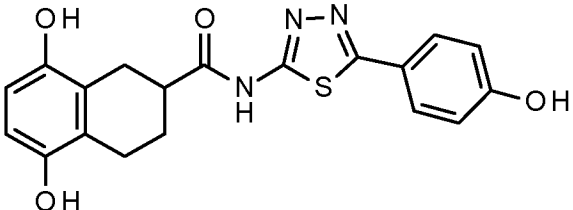
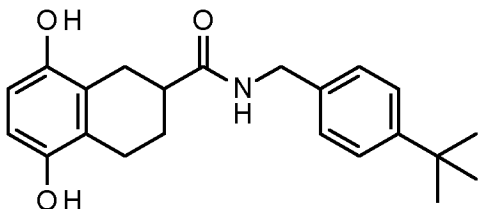
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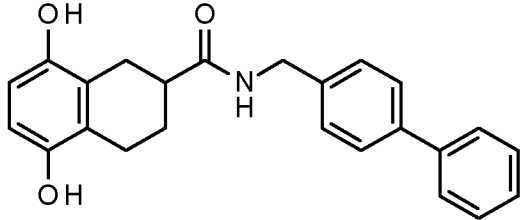
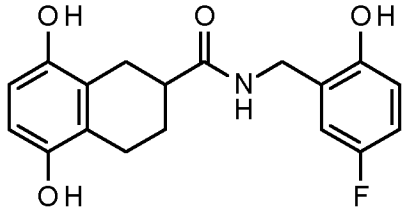
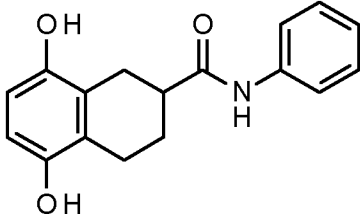
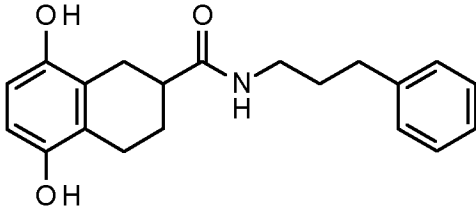
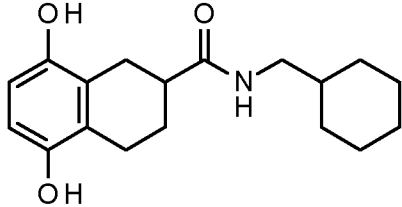
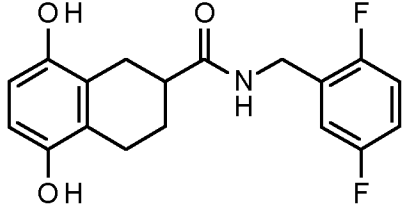
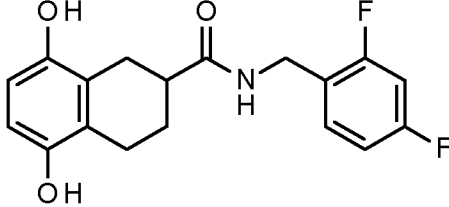
Step 4

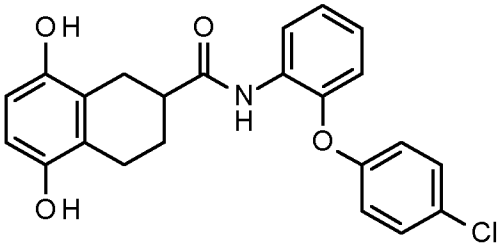
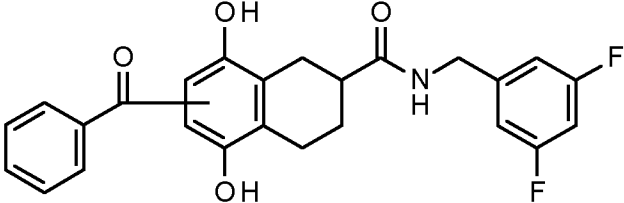
To a mixture of 5,8-dimethoxytetralin-1-carboxylic acid (100 mg, 0.423 mmol) and isobutylamine (31 mg, 0.423 mmol) in THF (5 mL) was added EDC (162 mg, 0.847 mmol), HOBt (68 mg, 0.508 mmol) and triethylamine (86 mg, 0.847 mmol, 118 µL) and stirred magnetically at room temperature under nitrogen atmosphere for 15 hours before being quenched with 10 % aq. citric acid (10 mL). The mixture was extracted with ethyl acetate (3 x 8 mL), combined organic extracts were washed with 10% aq. citric acid (2 x 7 mL), sat. aq. NaHCO<sub>3</sub> (3 x 8 mL), H<sub>2</sub>O (2 x 8 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified over silica gel with 0-100% ethyl acetate in cyclohexane, and with semi-preparative HPLC with 50 to 95% MeOH in H<sub>2</sub>O to yield N-isobutyl-5,8-dimethoxy-tetralin-1-carboxamide (14 mg, 0.048 mmol), Example 20, in 11% yield.

20

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
18		291.18	13.0	292 [M+H] <sup>+</sup>
19		263.15	7.7	264 [M+H] <sup>+</sup>
20		291.18	13.1	292 [M+H] <sup>+</sup>
21		313.17	12.9	312 [M-H] <sup>-</sup>
22		343.14	13.7	344 [M+H] <sup>+</sup>
23		333.12	11.0	334 [M+H] <sup>+</sup> 332 [M-H] <sup>-</sup>

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
24		297.14	10.4	298 [M+H] <sup>+</sup> 296 [M-H] <sup>-</sup>
25		433.11	12.5	434 [M+H] <sup>+</sup> 432 [M-H] <sup>-</sup>
26		311.15	11.2	312 [M+H] <sup>+</sup>
27		365.12	11.7	366 [M+H] <sup>+</sup> 364 [M-H] <sup>-</sup>
28		383.09	10.7	384 [M+H] <sup>+</sup> 382 [M-H] <sup>-</sup>
29		353.20	12.6	354 [M+H] <sup>+</sup> 352 [M-H] <sup>-</sup>

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
30		373.17		
31		331.12	10.2	332 [M+H] <sup>+</sup> 330 [M-H] <sup>-</sup>
32		283.12	10.5	284 [M+H] <sup>+</sup> 282 [M-H] <sup>-</sup>
33		325.17	8.5	326 [M+H] <sup>+</sup>
34		303.18	8.7	304 [M+H] <sup>+</sup>
35		33.12	7.7	334 [M+H] <sup>+</sup>
36		333.12	7.7	334 [M+H] <sup>+</sup>

Example	Structure	Exact mass (g/mol)	R <sub>t</sub> (min)	m/z
37		409.11	12.6	410 [M+H] <sup>+</sup> 408 [M-H] <sup>-</sup>
38		437.14	13.0	438 [M+H] <sup>+</sup> 436 [M-H] <sup>-</sup>

#### Biacore based DNA/Protein (*tetO*/TetR) interaction assay

##### *FortéBio's Octet Method*

- 5 The FortéBio technology (FortéBio, Inc., Menlo Park, CA, USA) is a novel label-free methodology for analyzing macromolecular ligand/capture interactions. The Octet system can be used to measure real-time, label-free analysis of biomolecular interactions and provide information on affinity, kinetics and concentration. The instrument is designed to assay up to eight samples in parallel in 2 min from a standard 96-well micro-plate. The
- 10 detection technology utilized in the Octet is based on Biolayer Interferometry (BLI). BLI relies on the reflective property of white light and is implemented in the Octet via the use of fiber optic-based biosensors. The biosensors are coated with molecules chosen to capture the targeted ligands. The measurements were performed on an Octet Red system equipped with streptavidin biosensor tips (SA). Tips were purchased from FortéBio.

15

##### *Interaction studies: FortéBio's Octet red*

- Interaction analyses were conducted at 30°C in running buffer (HBS-P + 5 mmol/L MgSO<sub>4</sub>) unless stated otherwise. (HBS-P buffer: 10 mM Hepes (pH 7.4), 150 mM NaCl, 0.005% (v/v) polysorbate P20, and 5 mmol/L MgSO<sub>4</sub>; a 10x HBS-P buffer from GE
- 20 Healthcare was used). Temperature control on the Octet was accomplished by holding the instrument at room temperature so that it could be heated to 30°C. Sensor tips were pre-wet for 10 min in running buffer immediately prior to use, and the micro plates used in the Octet were filled with 200 µl of sample or buffer per well and agitated at 600 rpm. For the experiments commercially available precoated streptavidine tips were used (SA).

Biotinylated oligos were loaded onto the FortéBio SA fibers in HBS-P buffer pH 7.4. Protein binding experiments were run with HBS-P buffer unless stated otherwise. After each run the tip was regenerated (maximum 4 times) with running buffer containing 0.3% w/v sodium dodecylsulfate (SDS).

5

#### Assay setup

Step		Time	Speed	Remarks
No.		s	rpm	
1	Baseline	180	1000	Running buffer
2	Loading TetO	900	600	50 nM in Running buffer
3	Baseline TetO	180	600	Running buffer
4	Association TetR	420	600	1 µg/mL in Running buffer
5	Dissociation TetR	240	600	Running buffer
6	Displacement Comp/TC	600	600	Compound 10 µg/mL & Tetracycline 10 ng/mL mix in Running Buffer
7	Baseline Comp/TC	180	600	Running buffer
8	Regeneration Step 1	5	1000	Running buffer & 0.3% SDS
9	Regeneration Step 2	5	1000	Running buffer
10	Regeneration Step 1	5	1000	Running buffer & 0.3% SDS
11	Regeneration Step 2	5	1000	Running buffer
12	Regeneration Step 1	5	1000	Running buffer & 0.3% SDS
13	Regeneration Step 2	5	1000	Running buffer
Next measurement starting at Step 3				

#### Microdilution assay in clinical patient isolates

##### 10 *Broth micro-dilution assay in cation-adjusted Mueller-Hinton (CA-MHB)*

The assay protocol is adapted from the *Clinical and Laboratory Standards Institute* (CLSI) standardized method for broth microdilution. This methodology was used to evaluate the susceptibility of pathogenic clinical isolates towards different antibiotics in combination with a compound of the invention.

15

Antibiotic-resistant *staphylococcal*, *enterococcal*, *enterobacterial* or *acinetobacter* isolates were scraped from fresh Orientation Agar plates, suspended in saline solution with the turbidity adjusted to OD<sub>610</sub> of 0.1 (corresponds to 0.5 McFarland scale). Subsequently, the cultures were diluted 160x in CA-MHB medium and a volume of 80 µl was dispensed into



each well of a 96 well microtiter plate. Plates were covered and incubated for 16 to 20 hours at 35°C without shaking. Plates were then visually analyzed, scanned and subsequently the OD<sub>610</sub> was determined. Average and standard deviations were calculated from at least two wells with the same condition. Values were normalized to the DMSO control (which is 100%).

#### Results:

Correlation of the synergistic effect of compounds of the invention with tetracyclines on bacterial growth inhibition (% growth relative to DMSO; 4 µg/ml tetracyclines and 10 µg/ml compounds of the invention) and TetR/tetO interaction (% association of TetR to tetO relative to DMSO). Bacterial growth was analysed 16 to 20 hours after inoculation according to CLSI guidelines. OD<sub>610</sub> was determined with a Tecan Infinite F200 and normalized to the DMSO control. The interaction of TRIC compounds with the TetR protein and the effect on TetR- tetO operator DNA binding was analyzed with a FortéBio's Octet red and normalized to the DMSO control.

Table

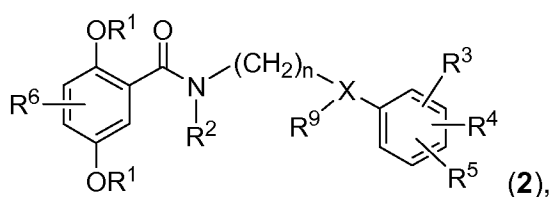
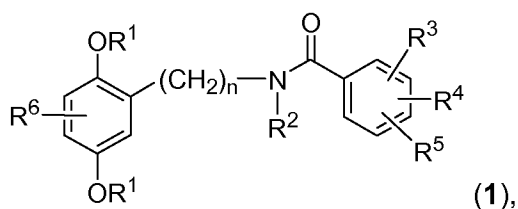
<b>Compound Ex. No.</b>	<b>Growth (% rel. to DMSO)</b>	<b>Association (% rel. to DMSO)</b>
1	55.20	15.84
2	34.40	51.60
3	41.10	63.20
4	63.87	
5	56.57	30.49
6	60.43	25.61
7	56.50	26.83
8	69.68	42.57
9	25.91	16.22
10	47.14	25.68
11	26.14	19.59
12	5.76	1.60
13	4.74	
14	18.21	10.26
15	4.88	85.19
16	6.15	2.52
17	8.11	70.49
18	103.70	13.64

19	11.50	54.02
20	63.75	97.40
21	25.77	
22	61.29	108.99
23	8.15	22.69
24	48.15	54.12
25	90.15	11.76
26	55.92	43.52
27	58.69	23.15
28	46.79	36.62
29	23.58	
30	15.00	25.35
31	68.68	20.42
32	58.27	25.35
33	16.62	19.05
34	13.58	21.09
35	25.80	30.61
36	33.52	27.89
37	10.42	14.18
38	21.92	37.31

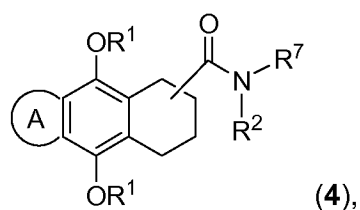
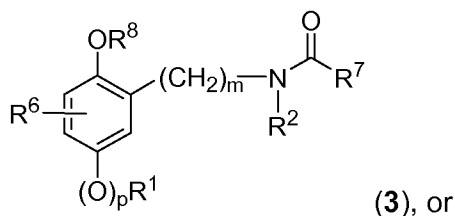
## Claims

1. A pharmaceutical composition comprising
  - (a) one or more tetracyclines;
  - (b) a TetR binding compound preventing TetR from dissociation of the *tetO* operator sequence in the presence of the inducing antibiotic tetracycline.
2. A pharmaceutical composition according to claim 1 wherein the TetR binding compound (b) is a compound of formula

10



15



wherein

- 20 R¹ is hydrogen or methyl;
- R² is hydrogen or methyl;
- R³, R⁴ and R⁵ are, independently of each other, hydrogen, lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, halo-lower alkoxy, phenoxy, amino, lower

alkylamino, di-(lower alkyl)amino, optionally substituted lower alkylcarbonylamino, carboxy, lower alkylcarbonyl, lower alkoxy, carbonyl, phenylcarbonyl, or phenyl;

R<sup>6</sup> is hydrogen, phenoxy or phenyl;

R<sup>7</sup> is alkyl, cyclohexyl-lower alkyl, optionally substituted phenyl or phenyl-lower alkyl, or

5 optionally substituted heteroaryl or heteroaryl-lower alkyl;

R<sup>8</sup> is hydrogen, methyl, phenyl or halophenyl;

A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the A ring connection, or absent;

X is CH or N;

10 R<sup>9</sup> is hydrogen or methyl, if X is CH; or R<sup>2</sup> and R<sup>9</sup> together represent ethylene, if X is N;

n is 1, 2, 3 or 4;

m is 0 or 1; and

p is 0 or 1.

15 3. A pharmaceutical composition according to claim 1 or 2, wherein the tetracycline (a) is selected from the group consisting of tetracycline, oxytetracycline, chlorotetracycline, demeclocycline, meclocycline, rolitetracycline, 6-thiatetracycline, 4-epi-anhydrochlor-tetracycline, aminomethylcycline, azatetracycline, fluorocycline, pentacycline, minocycline, doxycycline and tigecycline.

20

4. A pharmaceutical composition according to claim 2 or 3, wherein the TetR binding compound (b) is a compound of formula (1), (2), (3) and (4), wherein

R<sup>1</sup> is hydrogen or methyl;

R<sup>2</sup> is hydrogen or methyl;

25 R<sup>3</sup> and R<sup>4</sup> are, independently of each other, hydrogen, lower alkyl, halo-lower alkyl, halogen, cyano, lower alkoxy, optionally substituted lower alkylcarbonylamino, or phenyl;

R<sup>5</sup> is hydrogen, methyl, trifluoromethyl, fluorine, chlorine or cyano;

R<sup>6</sup> is hydrogen, phenoxy or phenyl;

R<sup>7</sup> is lower alkyl, cyclohexyl-lower alkyl, phenyl, unsubstituted or substituted by one, two

30 or three substituents selected from lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by one, two or three substituents selected from lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; or thiadiazolyl substituted by phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl;

35 R<sup>8</sup> is hydrogen, methyl, phenyl or halophenyl;

A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the A ring connection, or absent;

X is CH or N;

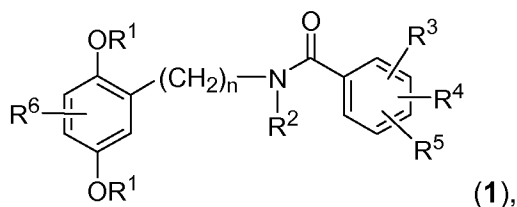
R<sup>9</sup> is hydrogen or methyl, if X is CH; or R<sup>2</sup> and R<sup>9</sup> together represent ethylene, if X is N;

n is 1, 2, 3 or 4;

m is 0 or 1; and

5 p is 0 or 1.

5. A pharmaceutical composition comprising a compound of formula (1),



wherein

10 R<sup>1</sup> is hydrogen or methyl;

R<sup>2</sup> is hydrogen or methyl;

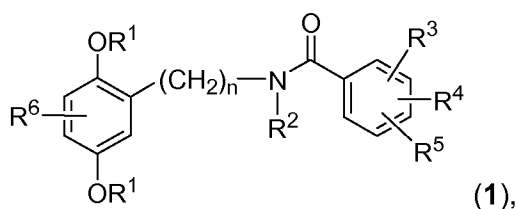
R<sup>3</sup> and R<sup>4</sup> are, independently of each other, hydrogen, lower alkyl, halo-lower alkyl, halogen, cyano, lower alkoxy, optionally substituted lower alkylcarbonylamino, or phenyl;

R<sup>5</sup> is hydrogen, methyl, trifluoromethyl, fluorine, chlorine or cyano;

15 R<sup>6</sup> is hydrogen, phenoxy or phenyl; and

n is 3 or 4.

6. A pharmaceutical composition comprising a compound of formula



20 wherein

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is hydrogen or methyl;

R<sup>3</sup> and R<sup>4</sup> are, independently of each other, hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano,

25 methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;

R<sup>5</sup> is hydrogen;

R<sup>6</sup> is hydrogen, phenoxy or phenyl; and

n is 1, 2, 3 or 4.

7. A pharmaceutical composition according to claim 6 comprising a compound of formula (1), wherein

$R^1$  is hydrogen;

$R^2$  is hydrogen or methyl;

5  $R^3$  is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, methoxy, ethoxy, methoxymethyl-carbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;

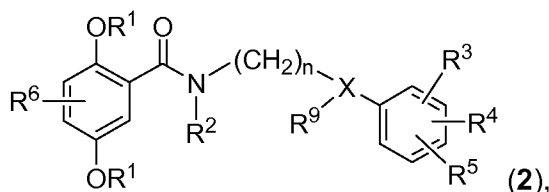
$R^4$  is fluoro or trifluoromethyl;

$R^5$  is hydrogen;

10  $R^6$  is hydrogen, phenoxy or phenyl; and

$n$  is 1, 2, 3 or 4.

8. A pharmaceutical composition comprising a compound of formula



15 wherein

$R^1$  is hydrogen;

$R^2$  is hydrogen or methyl;

$R^3$  and  $R^4$  are, independently of each other, hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;

20  $R^5$  is hydrogen; and

$R^6$  is hydrogen, phenoxy or phenyl;

$X$  is CH or N;

25  $R^9$  is hydrogen or methyl, if  $X$  is CH; or  $R^2$  and  $R^9$  together represent ethylene, if  $X$  is N;

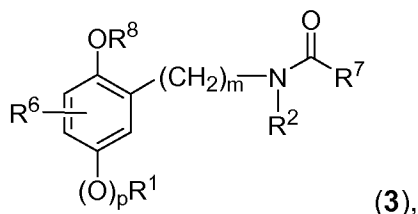
and

$n$  is 2, 3 or 4, if  $X$  is CH; or  $n$  is 2, if  $X$  is N.

9. A pharmaceutical composition according to claim 8 comprising a compound of formula

30 (2), wherein  $X$  is N and  $n$  is 2.

10. A pharmaceutical composition comprising a compound of formula



wherein

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is hydrogen or methyl;

5 R<sup>6</sup> is hydrogen, phenoxy or phenyl;

R<sup>7</sup> is lower alkyl or phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by lower alkyl, halo-lower alkyl, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl;

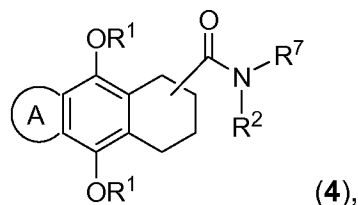
R<sup>8</sup> is hydrogen, methyl, phenyl or halophenyl;

m is 0 or 1; and

10 p is 0 or 1.

11. A pharmaceutical composition according to claim 10 comprising a compound of formula (3), wherein p is 0.

15 12. A pharmaceutical composition comprising a compound of formula



wherein

R<sup>1</sup> is hydrogen;

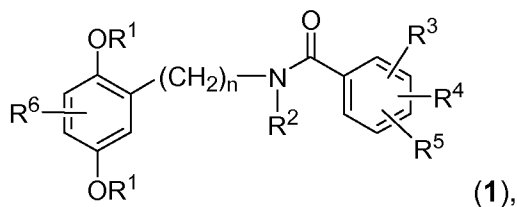
R<sup>2</sup> is hydrogen or methyl;

20 R<sup>7</sup> is lower alkyl, cyclohexyl-lower alkyl, phenyl, unsubstituted or substituted by one or two substituents selected from lower alkyl, halo-lower alkyl, halogen, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by one or two substituents selected from lower alkyl, halo-lower alkyl, halogen, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; or thiadiazolyl substituted by

25 phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl; and

A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the A ring connection, or absent.

13. A compound of formula



wherein

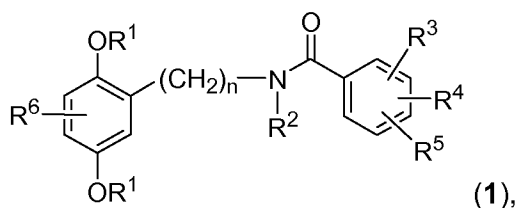
R¹ is hydrogen or methyl;

R² is hydrogen or methyl;

- 5 R³ and R⁴ are, independently of each other, hydrogen, lower alkyl, halo-lower alkyl, halogen, cyano, lower alkoxy, optionally substituted lower alkylcarbonylamino, or phenyl;  
 R⁵ is hydrogen, methyl, trifluoromethyl, fluorine, chlorine or cyano;  
 R⁶ is hydrogen, phenoxy or phenyl; and  
 n is 3 or 4.

10

14. A compound of formula

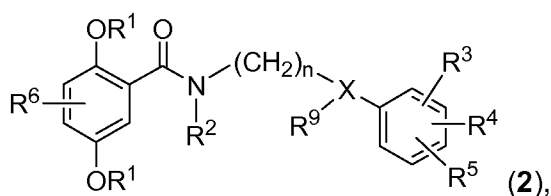


wherein

R¹ is hydrogen;

- 15 R² is hydrogen or methyl;  
 R³ is hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, hydroxy, methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;  
 20 R⁴ is fluoro or trifluoromethyl;  
 R⁵ is hydrogen;  
 R⁶ is hydrogen, phenoxy or phenyl; and  
 n is 1, 2, 3 or 4.

25 15. A compound of formula



wherein



$R^1$  is hydrogen;

$R^2$  is hydrogen or methyl;

$R^3$  and  $R^4$  are, independently of each other, hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, fluorine, chlorine, bromine, cyano, methoxy, ethoxy, methoxymethylcarbonylamino, cyanomethylcarbonylamino, or tert-butylaminomethylcarbonylamino;

$R^5$  is hydrogen; and

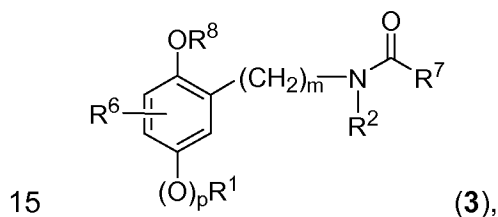
$R^6$  is hydrogen, phenoxy or phenyl;

X is CH or N;

$R^9$  is hydrogen or methyl, if X is CH; or  $R^2$  and  $R^9$  together represent ethylene, if X is N; and

n is 2, 3 or 4, if X is CH; or n is 2, if X is N.

16. A compound of formula



wherein

$R^1$  is hydrogen or methyl;

$R^2$  is hydrogen or methyl;

$R^6$  is hydrogen, phenoxy or phenyl;

$R^7$  is lower alkyl, cyclohexyl-lower alkyl, phenyl, unsubstituted or substituted by one, two or three substituents selected from lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by one, two or three substituents selected from lower alkyl, halo-lower alkyl, halogen, cyano, phenoxy, halophenoxy, or phenyl;

$R^8$  is hydrogen, methyl, phenyl or halophenyl;

m is 0 or 1; and

p is 0.

17. A compound according to claim 16 of formula (3), wherein

$R^1$  is hydrogen;

$R^2$  is hydrogen or methyl;

$R^6$  is hydrogen, phenoxy or phenyl;

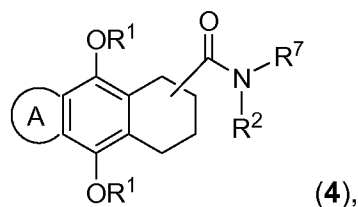
$R^7$  is lower alkyl or phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by lower alkyl, halo-lower alkyl, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl;

$R^8$  is hydrogen, methyl, phenyl or halophenyl;

m is 0 or 1; and

5 p is 0.

18. A compound of formula



wherein

10  $R^1$  is hydrogen or methyl;

$R^2$  is hydrogen or methyl;

$R^7$  is lower alkyl, cyclohexyl-lower alkyl, phenyl, unsubstituted or substituted by one, two or three substituents selected from lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; phenyl-lower alkyl, wherein phenyl is

15 unsubstituted or substituted by one, two or three substituents selected from lower alkyl, halo-lower alkyl, halogen, cyano, hydroxy, lower alkoxy, phenoxy, halophenoxy, or phenyl; or thiadiazolyl substituted by phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl; and

A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the

20 A ring connection, or absent.

19. A compound according to claim 18 of formula (4), wherein

$R^1$  is hydrogen;

$R^2$  is hydrogen or methyl;

25  $R^7$  is lower alkyl, cyclohexyl-lower alkyl; phenyl, unsubstituted or substituted by one or two substituents selected from lower alkyl, halo-lower alkyl, halogen, hydroxy, lower alkoxy, phenoxy, halophenoxy or phenyl; phenyl-lower alkyl, wherein phenyl is unsubstituted or substituted by one or two substituents selected from lower alkyl, halo-lower alkyl, halogen, hydroxy, lower alkoxy, phenoxy, halophenoxy or phenyl; or thiadiazolyl substituted by

30 phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl; and

A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the A ring connection, or absent.

20. A compound according to claim 19 of formula (4), wherein

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is hydrogen or methyl;

R<sup>7</sup> is n-butyl, sec-butyl, tert-butyl, n-propyl, isopropyl, ethyl, methyl, cyclohexylmethyl, cyclohexylethyl; phenyl, unsubstituted or substituted by one or two substituents selected  
5 from ethyl, methyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, fluorine, chlorine, hydroxy, methoxy, ethoxy, phenoxy, fluorophenoxy, chlorophenoxy or phenyl; phenylmethyl, 2-phenylethyl or 3-phenylpropyl, wherein phenyl is unsubstituted or substituted by one or two substituents selected from ethyl, methyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, fluorine, chlorine, hydroxy, methoxy, ethoxy, phenoxy,  
10 fluorophenoxy, chlorophenoxy or phenyl; or thiadiazolyl substituted by phenyl, trifluoromethylphenyl, halophenyl or hydroxyphenyl; and  
A is a benzo ring, 1,4-dioxobenzo ring, phenylcarbonyl in either of the two positions of the A ring connection, or absent.

15 21. Use of a pharmaceutical composition according to any one of claims 1 to 4 in a method for the prophylactic or therapeutic treatment of an infective bacterial disease.

22. Use of a compound according to any one of claims 13 to 20 or of a pharmaceutical composition according to any one of claims 5 to 12 in combination with one or more  
20 tetracyclines in a method for the prophylactic or therapeutic treatment of an infective bacterial disease.

23. A method of treatment of an infective bacterial disease comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition according to  
25 any one of claims 1 to 4.

24. A method of treatment of an infective bacterial disease comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 13 to 20 or of a pharmaceutical composition according to any one of claims 5 to 12 and  
30 one or more tetracyclines.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2014/052012

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K31/16 C07D241/02 A61P31/00	A61K31/165 C07C231/00
A61K31/166 C07C233/58	A61K31/167 C07C233/64	A61K31/4965 C07C235/46
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C07C C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARBOSA FILHO, JOSE M. ET AL: "Synthesis of several new phenylethylamides of substituted benzoic acids", QUIMICA NOVA, 13(4), 332-4 CODEN: QUNODK; ISSN: 0100-4042, 1990, XP008162972, the whole document compound II	2,21,23
X	CH 631 158 A5 (HOECHST A.-G., GEORGIA) 30 July 1982 (1982-07-30) the whole document page 4, column 2, lines 7,34 ----- -/-	2
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search  7 March 2014		Date of mailing of the international search report  14/05/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer  Jakobs, Andreas

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/052012

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>INGELA FRITZSON ET AL: "N-Substituted salicylamides as selective malaria parasite dihydroorotate dehydrogenase inhibitors", MEDCHEMCOMM, vol. 2, no. 9, 1 January 2011 (2011-01-01) , page 895, XP055066445, ISSN: 2040-2503, DOI: 10.1039/c1md00118c the whole document compounds 1,8,9</p> <p>-----</p>	2
X	<p>ORJALA J ET AL: "ADUNCAMIDE, A CYTOTOXIC AND ANTIBACTERIAL .BETA.-PHENYLETHYLAMINE-DERIVED AMIDE FROM PIPER ADUNCUM", NATURAL PRODUCT LETTERS, HARWOOD ACADEMIC PUBLISHERS, CHUR, CH, vol. 2, no. 3, 1 January 1993 (1993-01-01) , pages 231-236, XP008054324, ISSN: 1057-5634 the whole document</p> <p>-----</p>	2
X	<p>CHEN ET AL: "Amides with anti-platelet aggregation activity from Piper taiwanense", FITOTERAPIA, IDB HOLDING, MILAN, IT, vol. 78, no. 6, 23 August 2007 (2007-08-23), pages 414-419, XP022208878, ISSN: 0367-326X, DOI: 10.1016/J.FITOTE.2007.04.009 the whole document compounds 1-3</p> <p>-----</p>	2
X	<p>FR 2 783 519 A1 (SOD CONSEILS RECH APPLIC [FR]) 24 March 2000 (2000-03-24) the whole document page 7, lines 5-7 page 11, lines 19-21 page 14, lines 14-18; examples 1,3</p> <p>-----</p>	2
A	<p>EINHORN ET AL: "über N-Methylolverbindungen der Säureamide", JUSTUS LIEBIGS ANNALEN DER CHEMIE, VERLAG CHEMIE GMBH, WEINHEIM; DE, vol. 343, 1 January 1905 (1905-01-01), pages 223-263, XP008162892, ISSN: 0075-4617 page 237, paragraph 1</p> <p>-----</p>	14
X	<p>US 5 298 502 A (HALLING BLAIK P [US] ET AL) 29 March 1994 (1994-03-29) the whole document sentences 50-60; compound 8aj</p> <p>-----</p>	2,6
	-/--	

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/052012

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHUBERT H ET AL: "SYNTHESE UND OXYDATION VON UNSYMMETRISCH VERBRUECKTEN DIHYDROCHINONEN", JOURNAL FUER PRAKTISCHE CHEMIE, LEIPZIG, DE, vol. 319, no. 5, 1 January 1977 (1977-01-01), pages 745-754, XP000926698, ISSN: 0021-8383, DOI: 10.1002/PRAC.19773190509 the whole document compounds 2k,2l,2m,2o,3k,3l -----	13,14
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MCCASKILL, E. S. ET AL: "Electrochemical properties and mechanisms of action of developers in Spectra film", XP002698904, retrieved from STN Database accession no. 1989:621899 abstract -----	13,14
A	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GOVINDACHARI, T. R. ET AL: "The isoquinoline series. II. Synthesis of some 5,6-and 5,8-dimethoxyisoquinolines", XP002698905, retrieved from STN Database accession no. 1958:61211 abstract -----	13,14
A	JP 2 115838 A (FUJI PHOTO FILM CO., LTD., JAPAN) 27 April 1990 (1990-04-27) the whole document page 272; compounds 1-1 -----	13,14
X	CHOUHAN H S ET AL: "2D-quantitative structure property relationship study of N-(aryl)-2-thiophene-2-ylacetamide derivatives as antitubercular agents", ASIAN JOURNAL OF CHEMISTRY, CHEMIC PUBLISHING, SAHIBADAD, IN, vol. 22, no. 6, 1 January 2010 (2010-01-01), pages 4675-4680, XP008162976, ISSN: 0970-7077 the whole document compound 20 ----- -/--	2

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2014/052012

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 29 01 630 A1 (KONISHIROKU PHOTO INDUSTRY CO., LTD., JAPAN) 24 July 1980 (1980-07-24) the whole document page 34; compounds Hq-14 -----	13,14
A	SATOH T ET AL: "COMPARISON OF THE INHIBITORY ACTION OF SYNTHETIC CAPSAICIN ANALOGUES WITH VARIOUS NADH-UBIQUINONE OXIDOREDUCTASES", BIOCHIMICA ET BIOPHYSICA ACTA, ELSEVIER, NL, vol. 1273, no. 1, 1 January 1996 (1996-01-01), pages 21-30, XP001025937, ISSN: 0006-3002, DOI: 10.1016/0005-2728(95)00131-X the whole document compound 49 -----	13,14
A	FRÉNOIS: "Structure of EthR in a Ligand Bound Short Article Conformation Reveals Therapeutic Perspectives against Tuberculosis", MOLECULAR CELL,, vol. 16, no. 2, 1 January 2004 (2004-01-01), pages 301-307, XP055066761, the whole document -----	1
A	EVA-MARIA HENSSLER ET AL: "Tet repressor mutants with altered effector binding and allostery", FEBS JOURNAL, vol. 272, no. 17, 1 September 2005 (2005-09-01), pages 4487-4496, XP055066764, ISSN: 1742-464X, DOI: 10.1111/j.1742-4658.2005.04868.x the whole document -----	1
X	EP 2 008 530 A1 (SYMRISE GMBH & CO KG [DE] SYMRISE AG [DE]) 31 December 2008 (2008-12-31) the whole document claim 1 -----	2
A	ZAKERI BIJAN ET AL: "Chemical biology of tetracycline antibiotics", BIOCHEMISTRY AND CELL BIOLOGY. BIOCHIMIE ET BIOLOGIE CELLULAIRE, NRC RESEARCH PRESS, CA, vol. 86, no. 2, 1 April 2008 (2008-04-01), pages 124-136, XP002500431, ISSN: 0829-8211, DOI: 10.1139/008-002 the whole document -----	1

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2014/052012

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

5-7, 13, 14(completely); 1-4, 21-24(partially)

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.



**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 5-7, 13, 14(completely); 1-4, 21-24(partially)

A compound and pharmaceutical compositions comprising compounds of formula (1) and use thereof either alone or in combination with tetracyclines to treat infective bacterial diseases

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2. claims: 8, 9, 15(completely); 1-4, 21-24(partially)

A compound and pharmaceutical compositions comprising compounds of formula (2) and use thereof either alone or in combination with tetracyclines to treat infective bacterial diseases

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3. claims: 10, 11, 16, 17(completely); 1-4, 21-24(partially)

A compound and pharmaceutical compositions comprising compounds of formula (3) and use thereof either alone or in combination with tetracyclines to treat infective bacterial diseases

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4. claims: 12, 18-20(completely); 1-4, 21-24(partially)

A compound and pharmaceutical compositions comprising compounds of formula (4) and use thereof either alone or in combination with tetracyclines to treat infective bacterial diseases

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/052012

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH 631158	A5	30-07-1982	
FR 2783519	A1	24-03-2000	
		AT 233750 T	15-03-2003
		AU 766373 B2	16-10-2003
		AU 5631499 A	10-04-2000
		BR 9913904 A	03-07-2001
		CA 2344224 A1	30-03-2000
		CN 1324353 A	28-11-2001
		CZ 20011055 A3	16-01-2002
		DE 69905738 D1	10-04-2003
		DE 69905738 T2	18-03-2004
		DK 1115719 T3	30-06-2003
		EP 1115719 A2	18-07-2001
		EP 1318149 A1	11-06-2003
		ES 2194501 T3	16-11-2003
		FR 2783519 A1	24-03-2000
		HK 1042486 A1	25-02-2005
		HU 0103513 A2	29-05-2002
		IL 141998 A	25-09-2005
		JP 2002526493 A	20-08-2002
		MY 127537 A	29-12-2006
		NO 20011479 A	18-05-2001
		NZ 511189 A	26-09-2003
		PL 347480 A1	08-04-2002
		PT 1115719 E	31-07-2003
		RU 2238939 C2	27-10-2004
		US 6653312 B1	25-11-2003
		US 2005261269 A1	24-11-2005
		US 2006084667 A1	20-04-2006
		WO 0017190 A2	30-03-2000
		ZA 200103204 A	19-09-2002
US 5298502	A	29-03-1994	NONE
JP 2115838	A	27-04-1990	
DE 2901630	A1	24-07-1980	NONE
EP 2008530	A1	31-12-2008	EP 2008530 A1 31-12-2008
		US 2008317923 A1	25-12-2008