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(54) **CYSTOBACTAMIDES**

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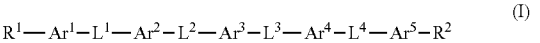
(57) **ABSTRACT**

The present invention provides cystobactamides of formula (I) and the use thereof for the treatment or prophylaxis of bacterial infections:



(I)

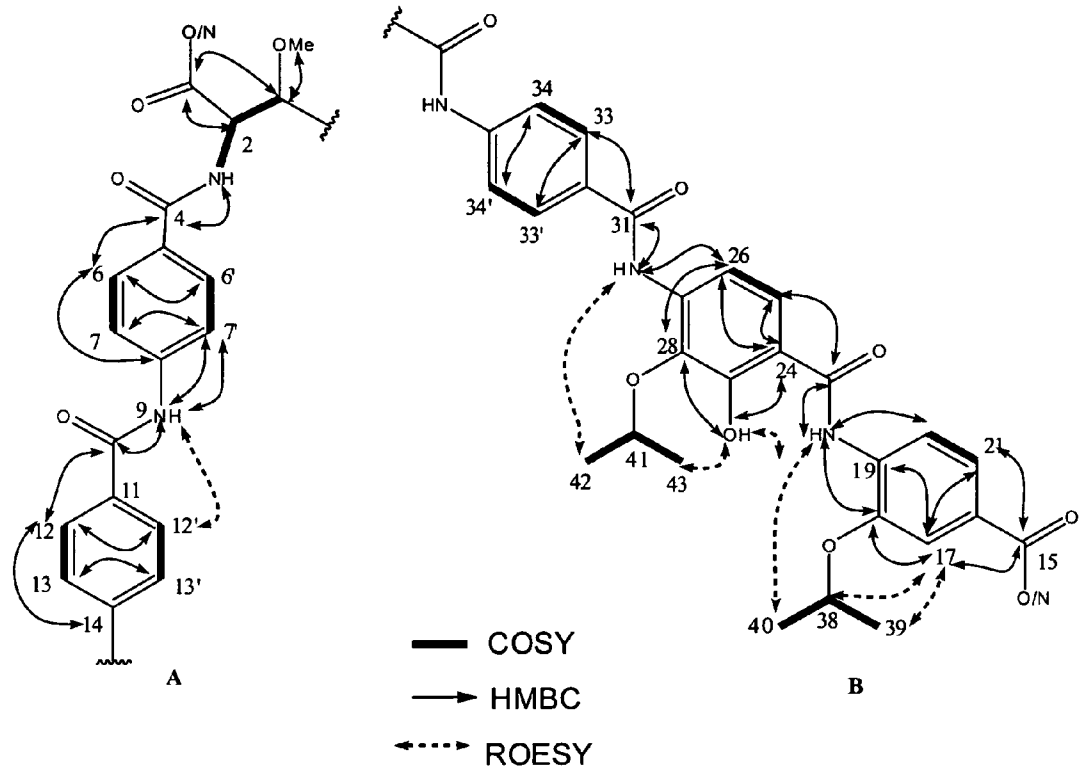


Figure 1

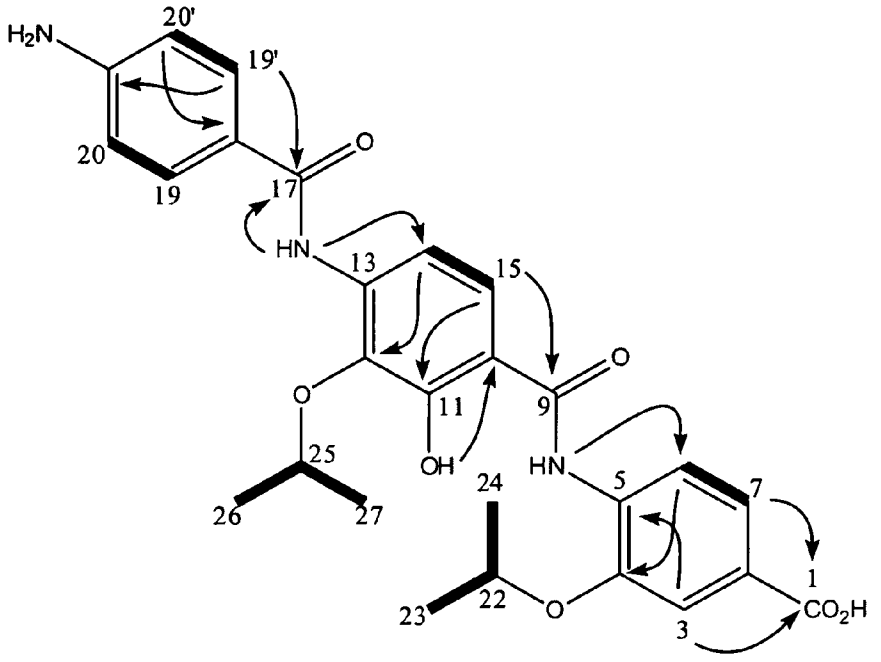

H2N
20'
19'
20
19
17
O
HN
13
15
O
11
9
O
25
OH
HN
5
7
24
26
27
1
CO2H
23
22
O
3

Figure 2

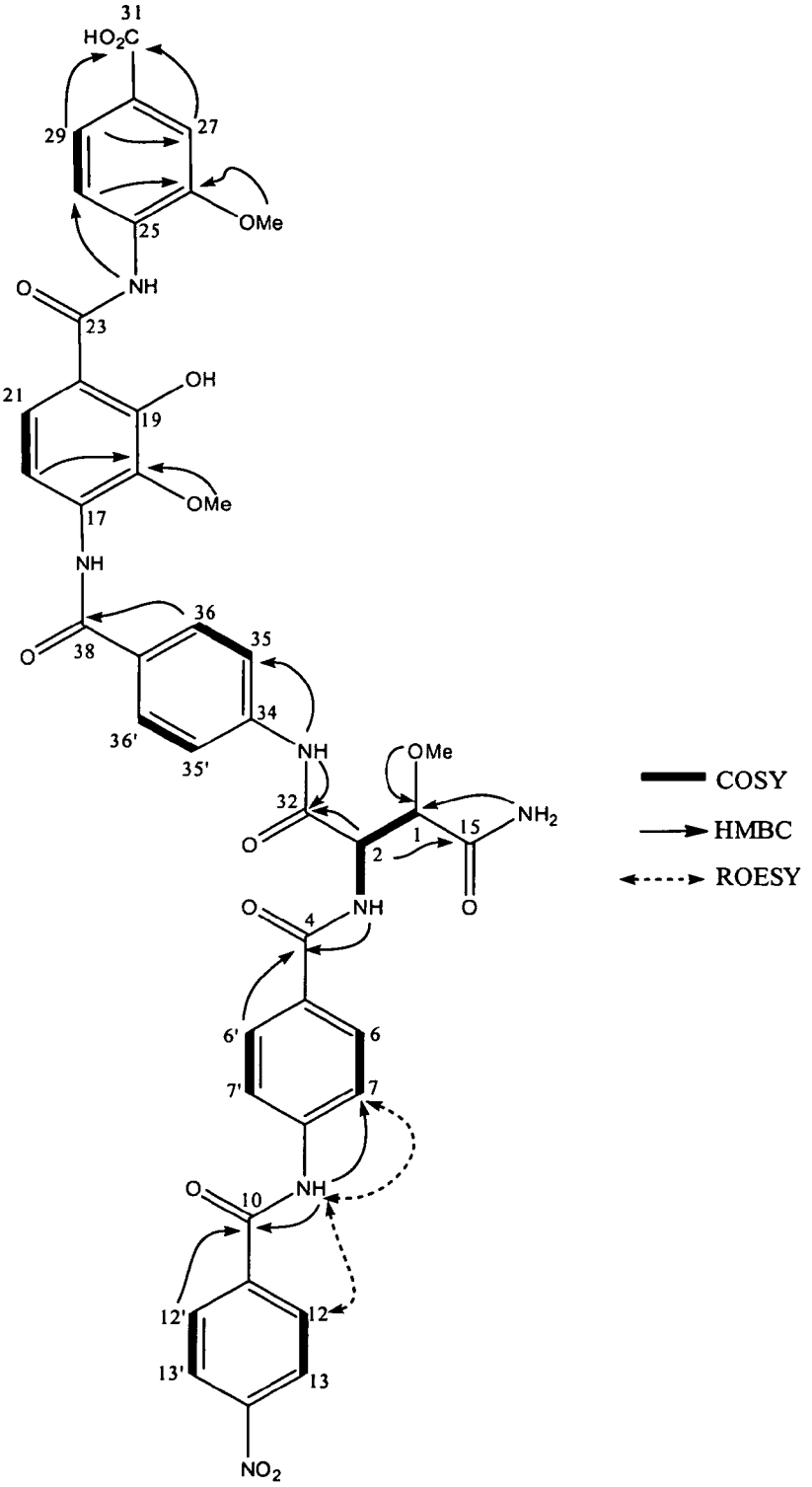

31
HO2C
29
27
OMe
25
NH
O
23
OH
21
19
OMe
17
NH
36
35
O
38
34
36'
35'
NH
OMe
32
NH2
1
15
2
O
O
NH
O
4
6'
6
7'
7
NH
O
10
12'
12
13'
13
NO2
COSY
HMBC
ROESY

Figure 3

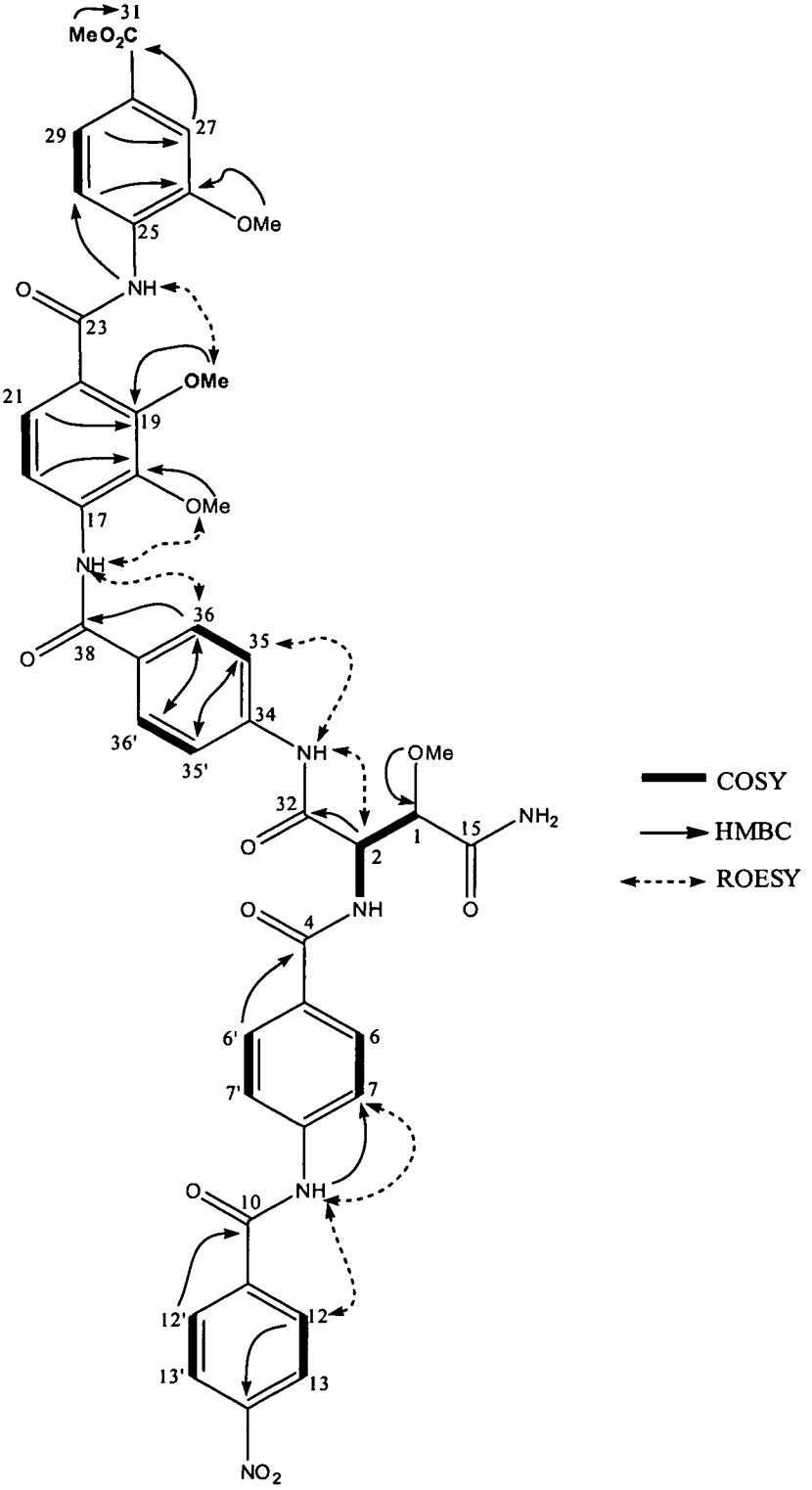

31
MeO2C
29
27
25
OMe
NH
O
23
OMe
21
19
OMe
17
NH
36
35
O
38
34
36'
35'
NH
OMe
32
O
2
1
15
NH2
O
NH
O
4
6'
6
7'
7
NH
O
10
12'
12
13'
13
NO2
COSY
HMBC
ROESY

Figure 4

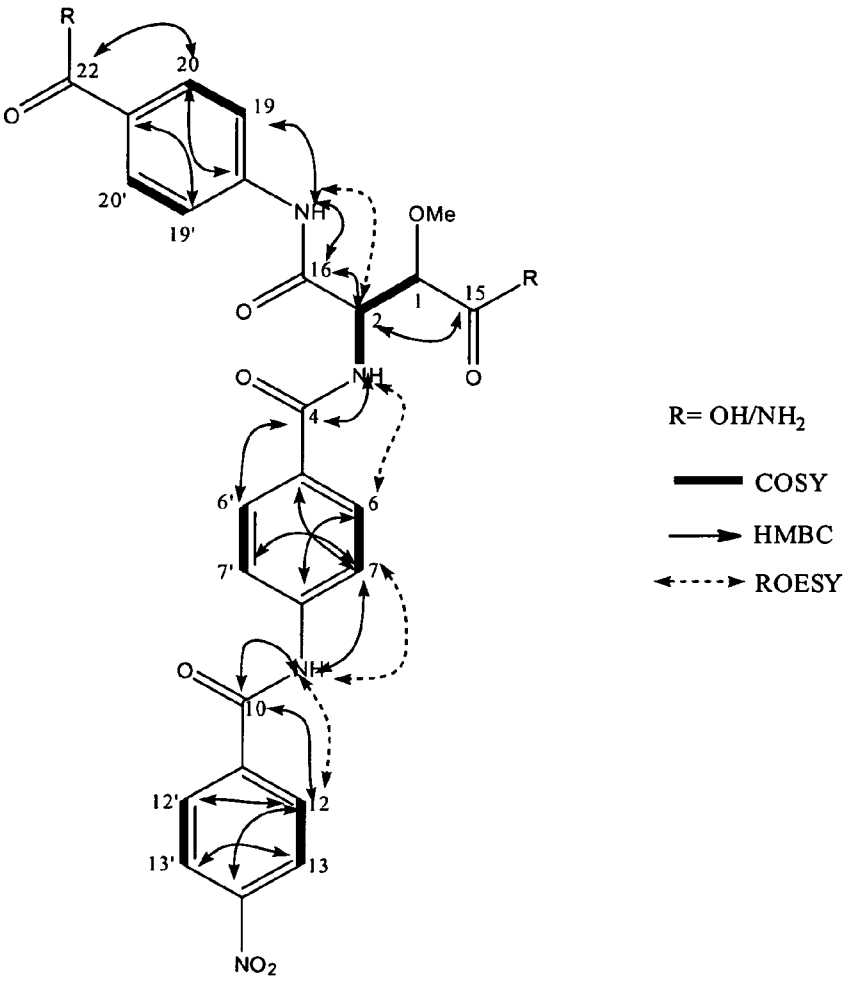

R
22
20
O
19
20'
19'
NH
OMe
16
O
1
15
R
2
O
NH
O
4
6'
6
7'
7
NH
O
10
12'
12
13'
13
NO2
R= OH/NH2
COSY
HMBC
ROESY

Figure 5

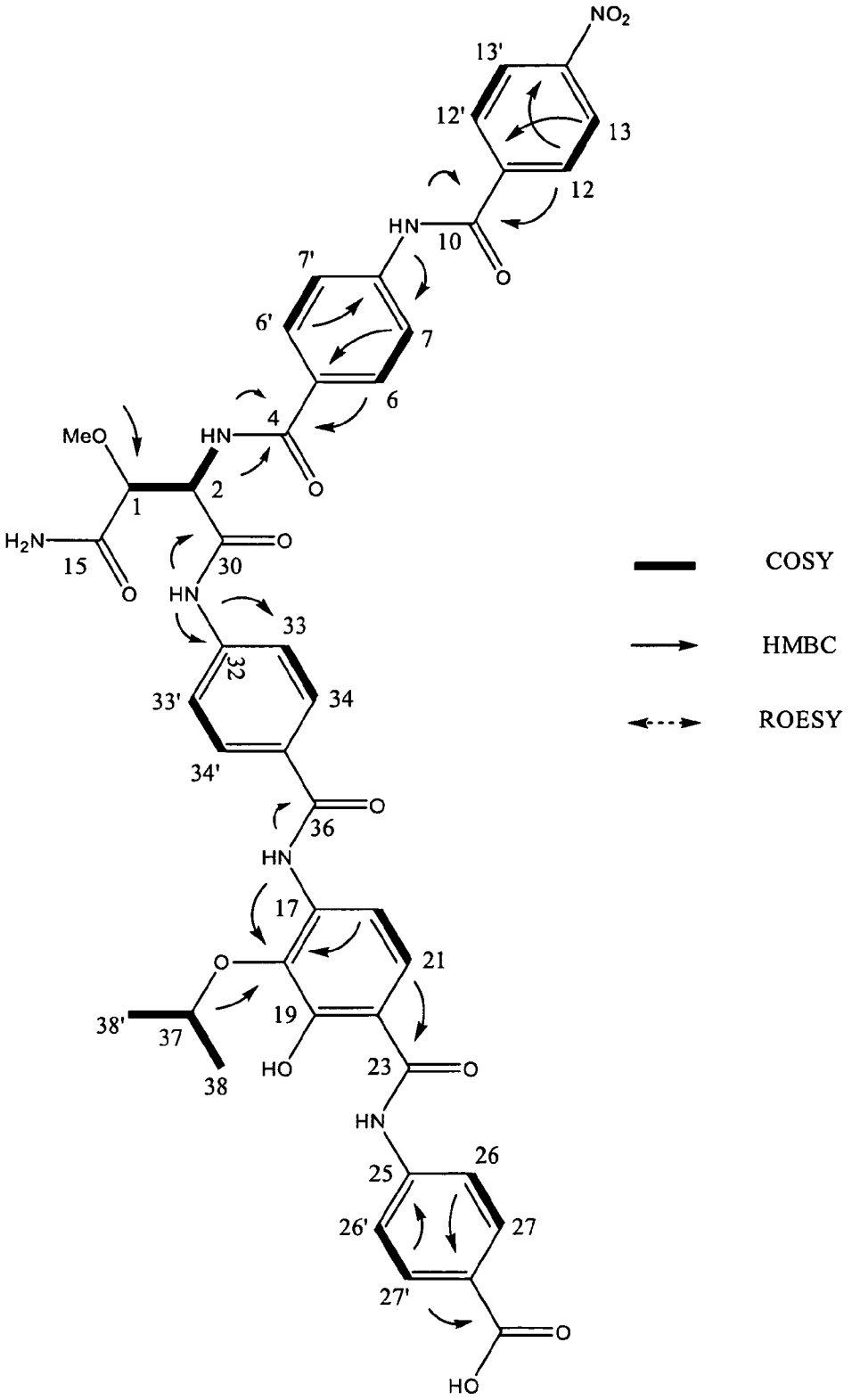

NO2
13'
12'
13
12
HN
10
O
7'
6'
7
6
4
HN
O
MeO
2
1
H2N
15
O
O
30
HN
33
32
33'
34
34'
O
36
HN
17
O
21
38'
37
19
38
HO
23
O
HN
25
26
26'
27
27'
O
HO
COSY
HMBC
ROESY

Figure 6

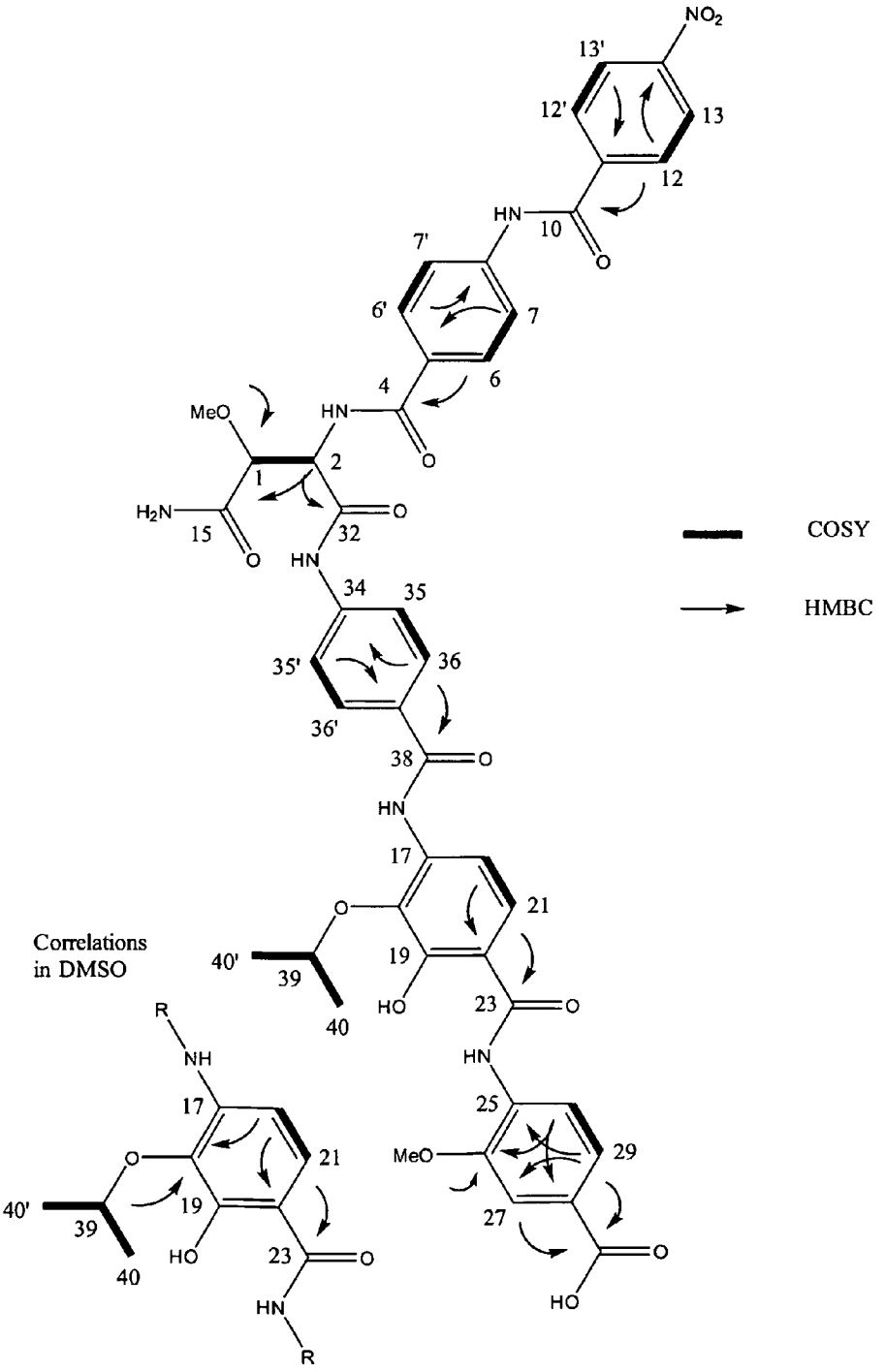

NO2
13'
12'
13
12
HN
10
O
7'
6'
7
6
4
HN
O
MeO
1
2
H2N
15
O
O
32
HN
34
35
35'
36
36'
38
O
HN
17
O
21
19
HO
23
O
HN
25
MeO
29
27
O
HO
40'
39
40
R
NH
17
O
21
19
HO
23
O
HN
R
40'
39
40
COSY
HMBC
Correlations
in DMSO

Figure 7

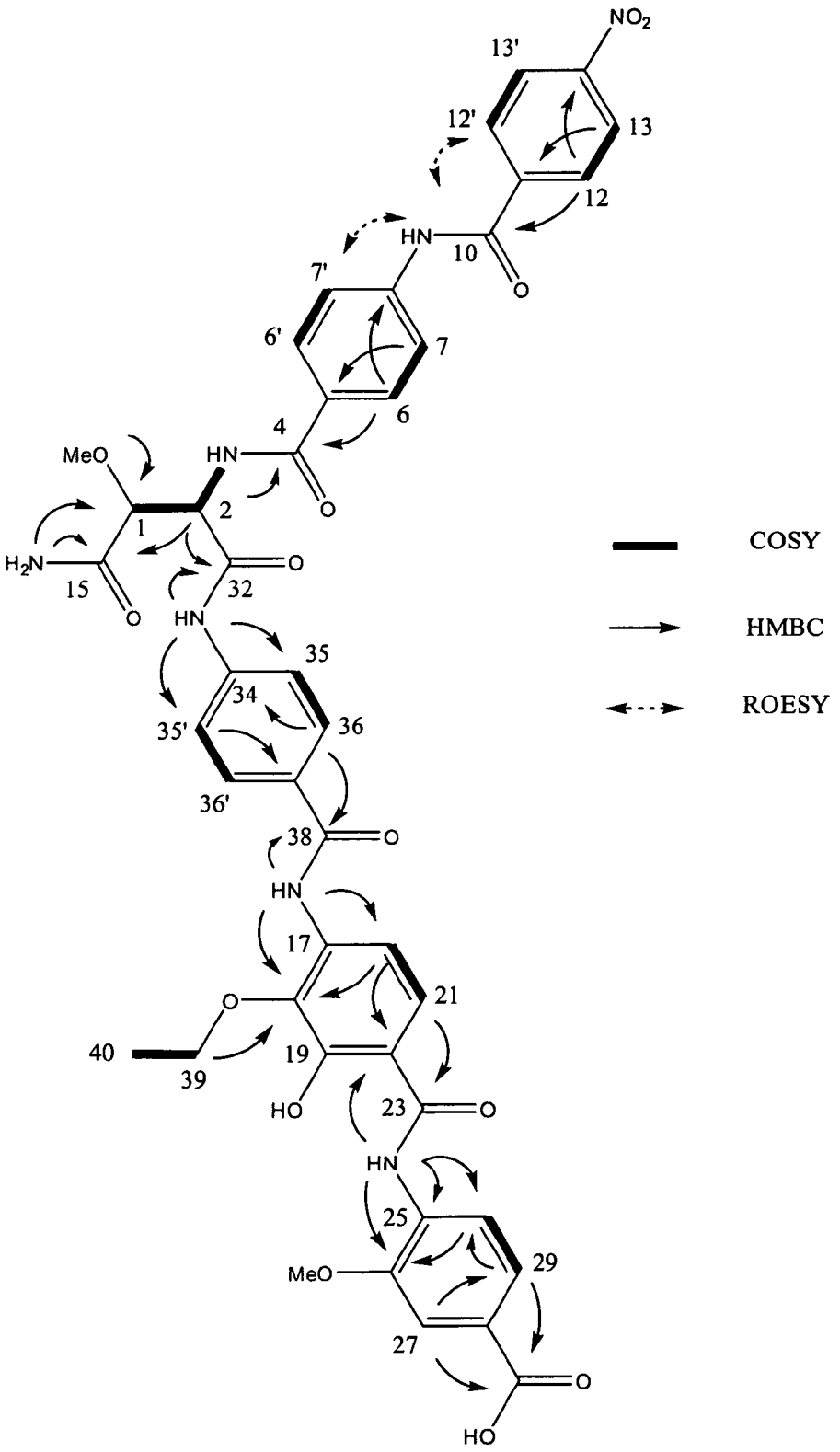

NO2
13'
12'
13
12
HN
10
O
7'
6'
7
6
4
HN
O
MeO
2
1
H2N
15
O
O
32
HN
35
34
35'
36
36'
38
O
HN
17
O
21
40
39
19
HO
23
O
HN
25
MeO
29
27
O
HO
COSY
HMBC
ROESY

Figure 8

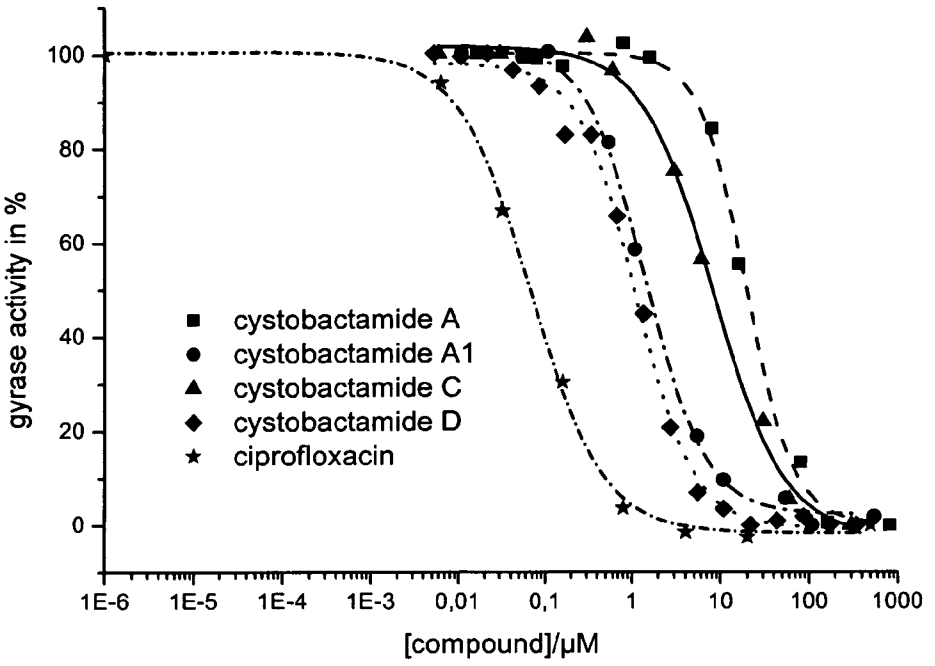

gyrase activity in %
100
80
60
40
20
0
cystobactamide A
cystobactamide A1
cystobactamide C
cystobactamide D
ciprofloxacin
1E-6
1E-5
1E-4
1E-3
0,01
0,1
1
10
100
1000
[compound]/µM

Figure 9a

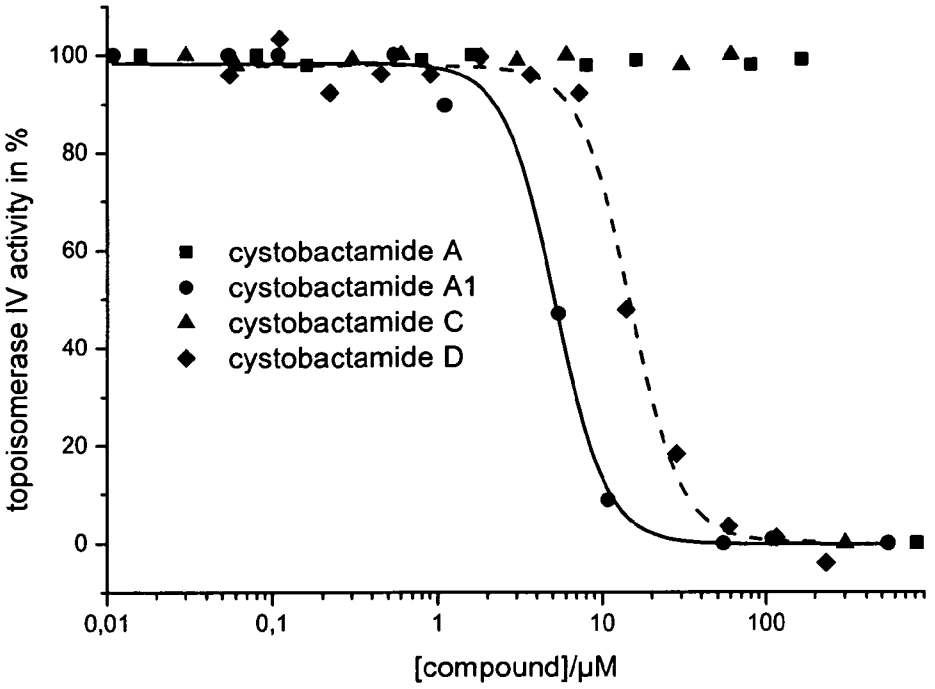

topoisomerase IV activity in %
100
80
60
40
20
0
0,01
0,1
1
10
100
[compound]/µM
cystobactamide A
cystobactamide A1
cystobactamide C
cystobactamide D

Figure 9b

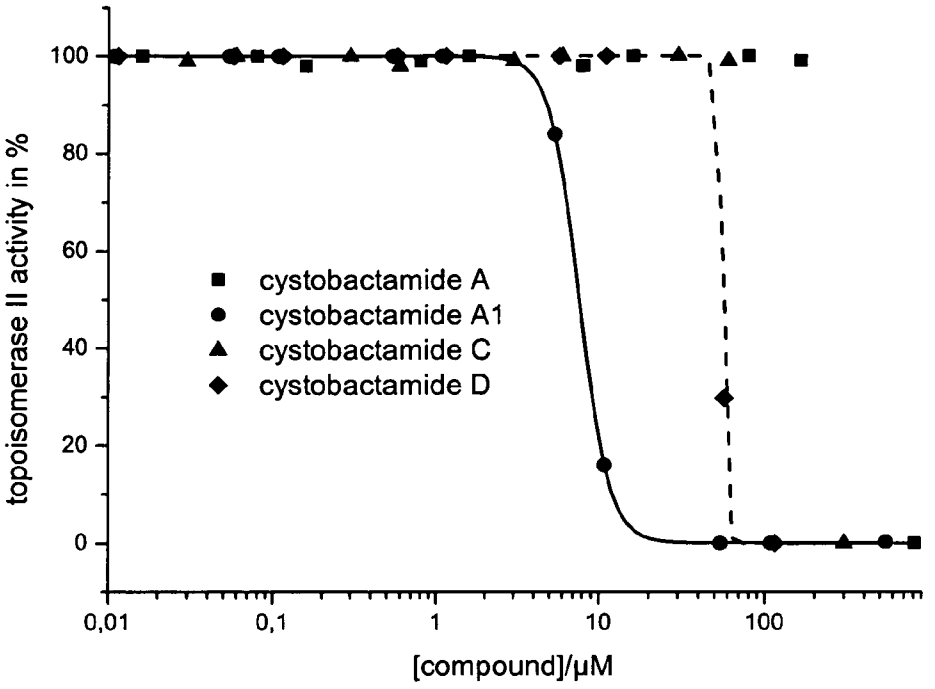

topoisomerase II activity in %
100
80
60
40
20
0
0,01
0,1
1
10
100
[compound]/µM
cystobactamide A
cystobactamide A1
cystobactamide C
cystobactamide D

Figure 9c

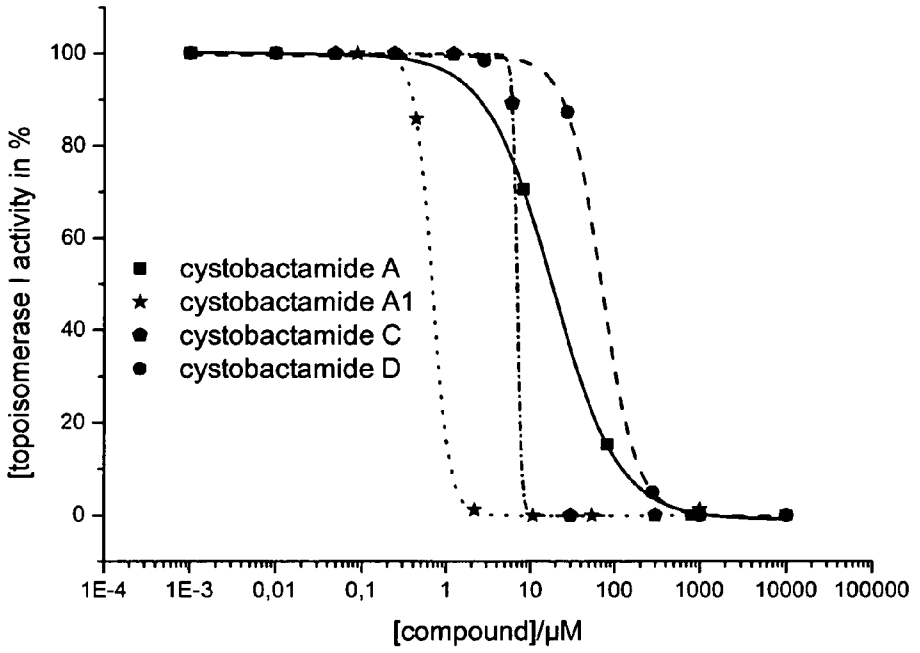

[topoisomerase I activity in %
100
80
60
40
20
0
cystobactamide A
cystobactamide A1
cystobactamide C
cystobactamide D
1E-4
1E-3
0,01
0,1
1
10
100
1000
10000
100000
[compound]/µM

Figure 9d

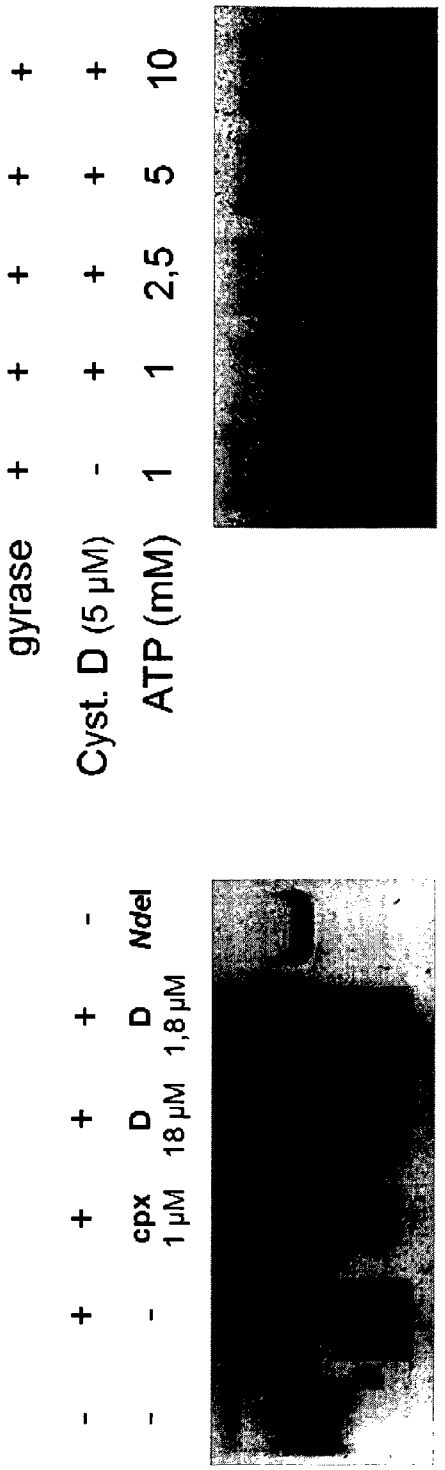
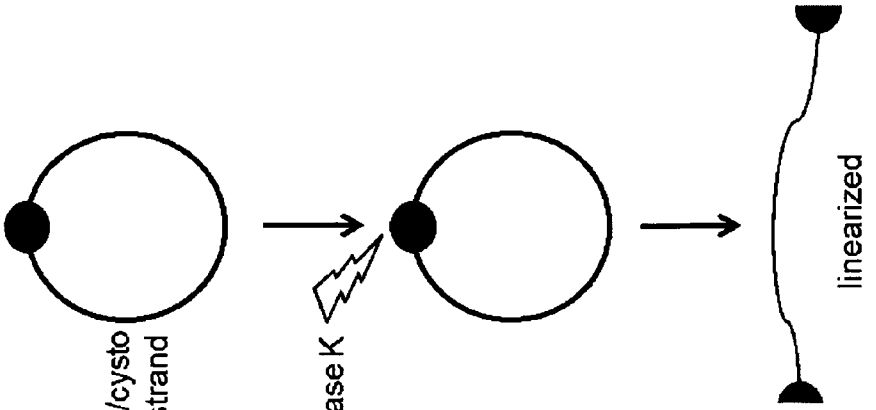
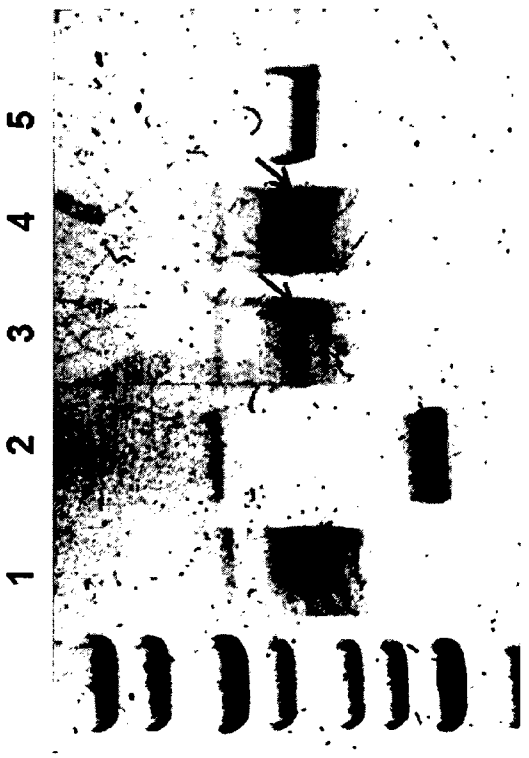


Figure 10 a and b





1: no Gyrase
2: standard rxn
3: Ciprofloxacin (100 µM
4: Cystobactamide D (100 µM)
5: *Nde*I-linearized plasmid

Figure 11

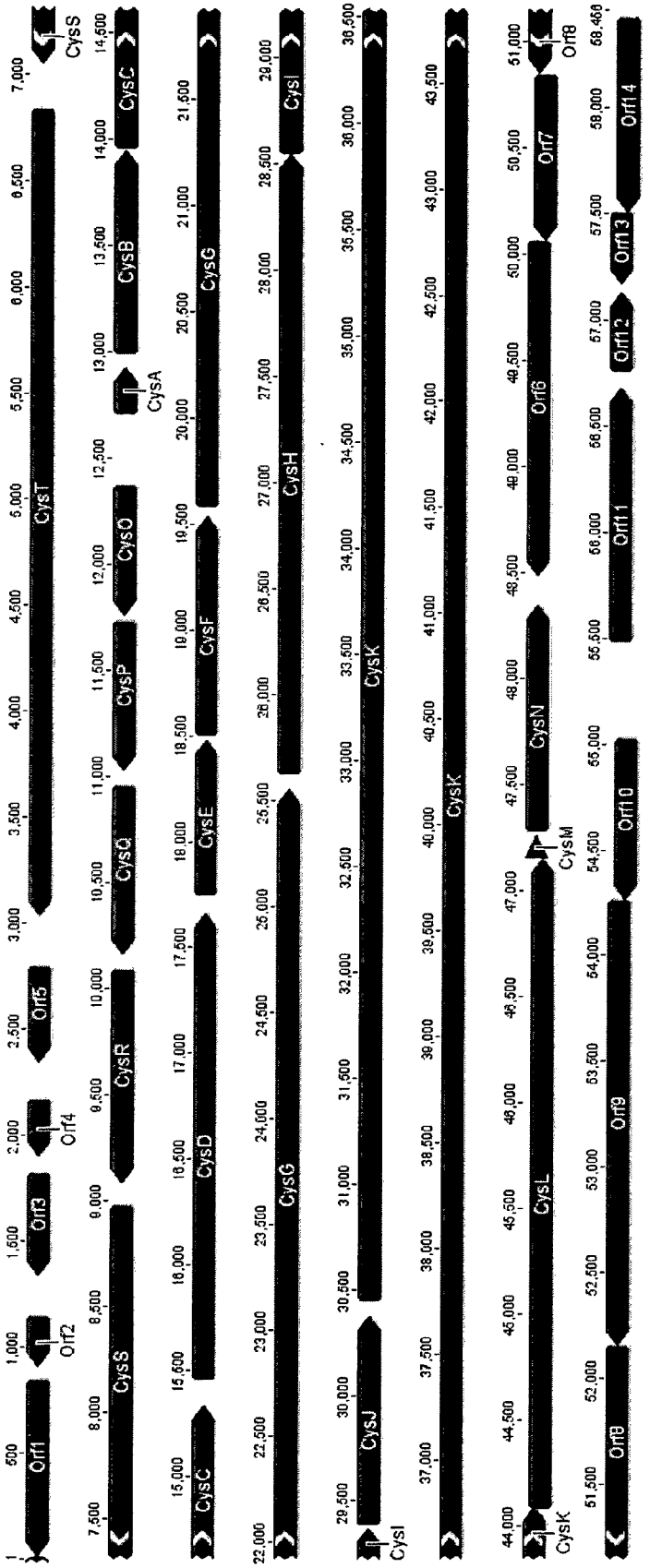
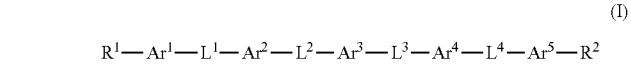

Orf1
Orf2
Orf3
Orf4
Orf5
CysT
CysS
CysC
CysA
CysB
CysO
CysP
CysR
CysQ
CysE
CysF
CysG
CysD
CysH
CysI
CysJ
CysK
CysN
CysM
CysL
Orf6
Orf7
Orf8
Orf9
Orf10
Orf11
Orf12
Orf13
Orf14

Figure 12

CYSTOBACTAMIDES

[0001] Cystobactamides are novel natural products that have been isolated from myxobacterium *Cystobacter velatus* (MCy8071; internal name: *Cystobacter ferrugineus*). Cystobactamides exhibit a good antibiotic activity, especially against selected Gram-negative bacteria, such as *E. coli, P. aeruginosa*, and *A. baumannii*, as well as a broad spectrum activity against Gram-positive bacteria.

[0002] The present invention provides compounds of formula (I)



(I)

wherein

[0003] Ar^1 is an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0004] Ar^2 is an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0005] Ar^3 is an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0006] Ar^4 is absent or an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0007] Ar^5 is absent or an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0008] L^1 is a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, —CNR^3—, —CO—, —SO—, —SO_2—, —SO_2NH—, —$NHSO_2$—, —SO_2NR^3—, —NR^3SO_2—, —$COCH_2$—, —CH_2CO—, —$COCR^3R^4$—, —CR^3R^4CO—, —NHCSNH—, —NR^3CSNR^4—, —CH═CH—, —CR^3═CR^4—, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

[0009] L^2 is a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, —CNR^3—, —CO—, —SO—, —SO_2—, —SO_2NH—, —$NHSO_2$—, —SO_2NR^3—, —NR^3SO_2—, —$COCH_2$—, —CH_2CO—, —$COCR^3R^4$—, —CR^3R^4CO—, —NHCSNH—, —NR^3CSNR^4—, —CH═CH—, —CR^3═CR^4—, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

[0010] L^3 is absent or a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, —CNR^3—, —CO—, —SO—, —SO_2—, —SO_2NH—, —$NHSO_2$—, —SO_2NR^3—, —NR^3SO_2—, —$COCH_2$—, —CH_2CO—, —$COCR^3R^4$—, —CR^3R^4CO—, —NHCSNH—, —NR^3CSNR^4—, —CH═CH—, —CR^3═CR^4—, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

[0011] L^4 is absent or a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, —CNR^3—, —CO—, —SO—, —SO_2—, —SO_2NH—, —$NHSO_2$—, —SO_2NR^3—, —NR^3SO_2—, —$COCH_2$—, —CH_2CO—, —$COCR^3R^4$—, —CR^3R^4CO—, —NHCSNH—, —NR^3CSNR^4—, —CH═CH—, —CR^3═CR^4—, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

[0012] R^1 is a hydrogen atom, a halogen atom, a hydroxy group, an amino group, a thiol group, a nitro group, a group of formula —COOH, —SO_2NH_2, —$CONH_2$, —NO_2 or —CN, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group;

[0013] R^2 is a hydrogen atom, a halogen atom, a hydroxy group, an amino group, a thiol group, a nitro group, a group of formula —COOH, —SO_2NH_2, —$CONH_2$, —NO_2 or —CN, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group;

[0014] the groups R^3 are independently from each other a hydrogen atom or a C_{1-6}alkyl group; and

[0015] the groups R^4 are independently from each other a hydrogen atom or a C_{1-6} alkyl group;

[0016] or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

[0017] The expression alkyl refers to a saturated, straight-chain or branched hydrocarbon group that contains from 1 to 20 carbon atoms, preferably from 1 to 15 carbon atoms, especially from 1 to 10 (e.g. 1, 2, 3 or 4) carbon atoms, for example a methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl, 2,2-dimethylbutyl or n-octyl group.

[0018] The expressions alkenyl and alkynyl refer to at least partially unsaturated, straight-chain or branched hydrocarbon groups that contain from 2 to 20 carbon atoms, preferably from 2 to 15 carbon atoms, especially from 2 to 10 (e.g. 2, 3 or 4) carbon atoms, for example an ethenyl (vinyl), propenyl (allyl), iso-propenyl, butenyl, ethinyl, propinyl, butinyl, acetylenyl, propargyl, isoprenyl or hex-2-enyl group. Preferably, alkenyl groups have one or two (especially preferably one) double bond(s), and alkynyl groups have one or two (especially preferably one) triple bond(s).

[0019] Furthermore, the terms alkyl, alkenyl and alkynyl refer to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl) such as, for example, a 2,2,2-trichioroethyl or a trifluoromethyl group.

[0020] The expression heteroalkyl refers to an alkyl, alkenyl or alkynyl group in which one or more (preferably 1 to 8; especially preferably 1, 2, 3 or 4) carbon atoms have been replaced by an oxygen, nitrogen, phosphorus, boron, selenium, silicon or sulfur atom (preferably by an oxygen, sulfur

or nitrogen atom) or by a SO or a SO_2 group. The expression heteroalkyl furthermore refers to a carboxylic acid or to a group derived from a carboxylic acid, such as, for example, acyl, acylalkyl, alkoxycarbonyl, acyloxy, acyloxyalkyl, carboxyalkylamide or al koxycarbonyloxy.

[0021] Preferably, a heteroalkyl group contains from 1 to 12 carbon atoms and from 1 to 8 heteroatoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). Especially preferably, a heteroalkyl group contains from 1 to 6 (e.g. 1, 2, 3 or 4) carbon atoms and 1, 2, 3 or 4 (especially 1, 2 or 3) heteroatoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen). The term C_1-C_6 heteroalkyl refers to a heteroalkyl group containing from 1 to 6 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and/or N (especially 0 and/or N). The term C_1-C_4 heteroalkyl refers to a heteroalkyl group containing from 1 to 4 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and/or N (especially 0 and/or N). Furthermore, the term heteroalkyl refers to groups in which one or more hydrogen atoms have been replaced by a halogen atom (preferably F or Cl).

[0022] Especially preferably, the expression heteroalkyl refers to an alkyl group as defined above (straight-chain or branched) in which one or more (preferably 1 to 6; especially preferably 1, 2, 3 or 4) carbon atoms have been replaced by an oxygen, sulfur or nitrogen atom; this group preferably contains from 1 to 6 (e.g. 1, 2, 3 or 4) carbon atoms and 1, 2, 3 or 4 (especially 1, 2 or 3) heteroatoms selected from oxygen, nitrogen and sulphur (especially oxygen and nitrogen); this group may preferably be substituted by one or more (preferably 1 to 6; especially preferably 1, 2, 3 or 4) fluorine, chlorine, bromine or iodine atoms or OH, =O, SH, =S, NH_2, =NH, N_3, CN or NO_2 groups.

[0023] The expression heteroalkylene group refers to a divalent heteroalkyl group.

[0024] Examples of heteroalkyl groups are groups of formulae: R^a—O—Y^a—, R^a—S—Y^a—, R^a—SO—Y^a—, R^a—SO_2—Y^a—, R^a—N(R^b)—Y^a—, R^a—CO—Y^a—, R^a—O—CO—Y^a—, R^a—CO—O—Y^a—, R^a—CO—N(R^b)—Y^a—, R^a—N(R^b)—CO—Y^a—, R^a—O—CO—N(R^b)—Y^a—, R^a—N(R^b)—CO—O—Y^a—, R^a—N(R^b)—CO—N(R^c)—Y^a—, R^a—O—CO—O—Y^a—, R^a—N(R^b)—C(=NR^d)—N(R^c)—Y^a—, R^a—CS—Y^a—, R^a—O—CS—Y^a—, R^a—CS—O—Y^a—, R^a—CS—N(R^b)—Y^a—, R^a—N(R^b)—CS—Y^a—, R^a—O—CS—N(R^b)—Y^a—, R^a—N(R^b)—CS—O—Y^a—, R^a—N(R^b)—CS—N(R^c)—Y^a—, R^a—O—CS—O—Y^a—, R^a—S—CO—Y^a—, R^a—CO—S—Y^a—, R^a—S—CO—N(R^b)—Y^a—, R^a—N(R^b)—CO—S—Y^a—, R^a—S—CO—O—Y^a—, R^a—O—CO—S—Y^a—, R^a—S—CO—S—Y^a—, R^a—S—CS—Y^a—, R^a—CS—S—Y^a—, R^a—S—CS—N(R^b)—Y^a—, R^a—N(R^b)—CS—S—Y^a—, R^a—S—CS—O—Y^a—, R^a—O—CS—S—Y^a—, wherein R^a being a hydrogen atom, a C_1-C_6 alkyl, a C_2-C_6 alkenyl or a C_2-C_6 alkynyl group; R^b being a hydrogen atom, a C_1-C_6 alkyl, a C_2-C_6 alkenyl or a C_2-C_6 alkynyl group; R^d being a hydrogen atom, a C_1-C_6 alkyl, a C_2-C_6 alkenyl or a C_2-C_6 alkynyl group; R^d being a hydrogen atom, a C_1-C_6 alkyl, a C_2-C_6 alkenyl or a C_2-C_6 alkynyl group and Ya being a bond, a C_1-C_6 alkylene, a C_2-C_6 alkenylene or a C_2-C_6 alkynylene group, wherein each heteroalkyl group contains at least one carbon atom and one or more hydrogen atoms may be replaced by fluorine or chlorine atoms.

[0025] Specific examples of heteroalkyl groups are methoxy, trifluoromethoxy, ethoxy, n-propyloxy, isopropyloxy, butoxy, tert-butyloxy, methoxymethyl, ethoxymethyl, —CH_2CH_2OH, —CH_2OH, —SO_2Me, methoxyethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-ethoxyethyl, methylamino, ethylamino, propylamino, isopropylamino, dimethylamino, diethylamino, isopropylethylamino, methylamino methyl, ethylamino methyl, diisopropylamino ethyl, methylthio, ethylthio, isopropylthio, enol ether, dimethylamino methyl, dimethylamino ethyl, acetyl, propionyl, butyryloxy, acetyloxy, methoxycarbonyl, ethoxycarbonyl, propionyloxy, acetylamino or propionylamino, carboxymethyl, carboxyethyl or carboxypropyl, N-ethyl-N-methylcarbamoyl or N-methylcarbamoyl. Further examples of heteroalkyl groups are nitrile, isonitrile, cyanate, thiocyanate, isocyanate, isothiocyanate and alkylnitrile groups.

[0026] The expression cycloalkyl refers to a saturated or partially unsaturated (for example, a cycloalkenyl group) cyclic group that contains one or more rings (preferably 1 or 2), and contains from 3 to 14 ring carbon atoms, preferably from 3 to 10 (especially 3, 4, 5, 6 or 7) ring carbon atoms. The expression cycloalkyl refers furthermore to groups in which one or more hydrogen atoms have been replaced by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH, N_3 or NO_2 groups, thus, for example, cyclic ketones such as, for example, cyclohexanone, 2-cyclohexenone or cyclopentanone. Further specific examples of cycloalkyl groups are a cyclopropyl, cyclobutyl, cyclopentyl, spiro[4,5]decanyl, norbornyl, cyclohexyl, cyclopentenyl, cyclohexadienyl, decalinyl, bicyclo[4.3.0]nonyl, tetraline, cyclopentylcyclohexyl, fluorocyclohexyl or cyclohex-2-enyl group.

[0027] The expression heterocycloalkyl refers to a cycloalkyl group as defined above in which one or more (preferably 1, 2 or 3) ring carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom) or a SO group or a SO_2 group. A heterocycloalkyl group has preferably 1 or 2 ring(s) containing from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms (preferably selected from C, O, N and S). The expression heterocycloalkyl refers furthermore to groups that are substituted by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH, N_3 or NO_2 groups. Examples are a piperidyl, prolinyl, imidazolidinyl, piperazinyl, morpholinyl, urotropinyl, pyrrolidinyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrofuryl or 2-pyrazolinyl group and also lactames, lactones, cyclic imides and cyclic anhydrides.

[0028] The expression alkylcycloalkyl refers to groups that contain both cycloalkyl and also alkyl, alkenyl or alkynyl groups in accordance with the above definitions, for example alkylcycloalkyl, cycloalkylalkyl, alkylcycloalkenyl, alkenylcycloalkyl and alkynylcycloalkyl groups. An alkylcycloalkyl group preferably contains a cycloalkyl group that contains one or two rings having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring carbon atoms, and one or two alkyl, alkenyl or alkynyl groups (especially alkyl groups) having 1 or 2 to 6 carbon atoms.

[0029] The expression heteroalkylcycloalkyl refers to alkylcycloalkyl groups as defined above in which one or more (preferably 1, 2 or 3) carbon atoms have been replaced by an oxygen, nitrogen, silicon, selenium, phosphorus or sulfur atom (preferably by an oxygen, sulfur or nitrogen atom) or a SO group or a SO_2 group. A heteroalkylcycloalkyl group

preferably contains 1 or 2 rings having from 3 to 10 (especially 3, 4, 5, 6 or 7) ring atoms, and one or two alkyl, alkenyl, alkynyl or heteroalkyl groups (especially alkyl or heteroalkyl groups) having from 1 or 2 to 6 carbon atoms. Examples of such groups are alkylheterocycloalkyl, alkylheterocycloalkenyl, alkenyl-heterocycloalkyl, alkynylheterocycloalkyl, heteroalkylcycloalkyl, heteroalkylhetero-cycloalkyl and heteroalkylheterocycloalkenyl, the cyclic groups being saturated or mono-, di- or tri-unsaturated.

[0030] The expression aryl refers to an aromatic group that contains one or more rings containing from 6 to 14 ring carbon atoms, preferably from 6 to 10 (especially 6) ring carbon atoms. The expression aryl refers furthermore to groups that are substituted by fluorine, chlorine, bromine or iodine atoms or by OH, SH, NH_2, N_3 or NO_2 groups. Examples are the phenyl, naphthyl, biphenyl, 2-fluorophenyl, anilinyl, 3-nitrophenyl or 4-hydroxyphenyl group.

[0031] The expression heteroaryl refers to an aromatic group that contains one or more rings containing from 5 to 14 ring atoms, preferably from 5 to 10 (especially 5 or 6 or 9 or 10) ring atoms, and contains one or more (preferably 1, 2, 3 or 4) oxygen, nitrogen, phosphorus or sulfur ring atoms (preferably 0, S or N). The expression heteroaryl refers furthermore to groups that are substituted by fluorine, chlorine, bromine or iodine atoms or by OH, SH, N_3, NH_2 or NO_2 groups. Examples are pyridyl (e.g. 4-pyridyl), imidazolyl (e.g. 2-imidazolyl), phenylpyrrolyl (e.g. 3-phenylpyrrolyl), thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, isoxazolyl, indazolyl, indolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, pyridazinyl, quinolinyl, isoquinolinyl, pyrrolyl, purinyl, carbazolyl, acridinyl, pyrimidyl, 2,3'-bifuryl, pyrazolyl (e.g. 3-pyrazolyl) and isoquinolinyl groups.

[0032] The expression aralkyl refers to groups containing both aryl and also alkyl, alkenyl, alkynyl and/or cycloalkyl groups in accordance with the above definitions, such as, for example, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, arylcycloalkenyl, alkylarylcycloalkyl and alkylarylcycloalkenyl groups. Specific examples of aralkyls are toluene, xylene, mesitylene, styrene, benzyl chloride, o-fluorotoluene, 1H-indene, tetraline, dihydronaphthalene, indanone, phenylcyclopentyl, cumene, cyclohexylphenyl, fluorene and indane. An aralkyl group preferably contains one or two aromatic ring systems (especially 1 or 2 rings), each containing from 6 to 10 carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing from 1 or 2 to 6 carbon atoms and/or a cycloalkyl group containing 5 or 6 ring carbon atoms.

[0033] The expression heteroaralkyl refers to groups containing both aryl or heteroaryl, respectively, and also alkyl, alkenyl, alkynyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups in accordance with the above definitions. A heteroaralkyl group preferably contains one or two aromatic ring systems (especially 1 or 2 rings), each containing from 5 or 6 to 9 or 10 ring carbon atoms and one or two alkyl, alkenyl and/or alkynyl groups containing 1 or 2 to 6 carbon atoms and/or one or two heteroalkyl groups containing 1 to 6 carbon atoms and 1, 2 or 3 heteroatoms selected from O, S and N and/or one or two cycloalkyl groups each containing 5 or 6 ring carbon atoms and/or one or two heterocycloalkyl groups, each containing 5 or 6 ring atoms comprising 1, 2, 3 or 4 oxygen, sulfur or nitrogen atoms.

[0034] Examples are arylheteroalkyl, arylheterocycloalkyl, arylheterocycloalkenyl, arylalkyl-heterocycloalkyl, arylalkenylheterocycloalkyl, arylalkynylheterocycloalkyl, arylalkyl-heterocycloalkenyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroaryl-heteroalkyl, heteroarylcycloalkyl, heteroarylcycloalkenyl, heteroarylheterocycloalkyl, heteroarylheterocycloalkenyl, heteroarylalkylcycloalkyl, heteroarylalkylheterocyclo-alkenyl, heteroarylheteroalkylcycloalkyl, heteroarylheteroalkylcycloalkenyl and heteroarylheteroalkylheterocycloalkyl groups, the cyclic groups being saturated or mono-, di- or tri-unsaturated. Specific examples are a tetrahydroisoquinolinyl, benzoyl, 2- or 3-ethylindolyl, 4-methylpyridino, 2-, 3- or 4-methoxyphenyl, 4-ethoxy-phenyl, 2-, 3- or 4-carboxyphenylalkyl group.

[0035] As already stated above, the expressions cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aryl, heteroaryl, aralkyl and heteroaralkyl also refer to groups that are substituted by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH, N_3 or NO_2 groups.

[0036] The expression "optionally substituted" especially refers to groups that are optionally substituted by fluorine, chlorine, bromine or iodine atoms or by OH, =O, SH, =S, NH_2, =NH, N_3 or NO_2 groups. This expression refers furthermore to groups that may be substituted by one, two, three or more unsubstituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} heteroalkyl, C_3-C_{18} cycloalkyl, C_2-C_{17} heterocycloalkyl, C_4-C_{20} alkylcycloalkyl, C_2-C_{19} heteroalkylcycloalkyl, C_6-C_{18} aryl, C_1-C_{17} heteroaryl, C_7-C_{20} aralkyl or C_2-C_{19} heteroaralkyl groups. This expression refers furthermore especially to groups that may be substituted by one, two, three or more unsubstituted C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_{10} cycloalkyl, C_2-C_9 heterocycloalkyl, C_7-C_{12} alkylcycloalkyl, C_2-C_{11} heteroalkylcycloalkyl, C_6-C_{10} aryl, C_1-C_9 heteroaryl, C_7-C_{12} aralkyl or C_2-C_{11} heteroaralkyl groups.

[0037] Especially preferably at group Ar^1, Ar^2, Ar^3, Ar^4 and Ar^5, the expression "optionally substituted" refers to groups that are optionally substituted by one, two or three groups independently selected from halogen atoms, hydroxy groups, groups of formula —O-alkyl (e.g. —O—C_{1-6} alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), —NH_2, —$NR^{5a}R^{6a}$ (wherein R^{5a} and R^{6a} independently from each other are a hydrogen atom or an alkyl group such as a C_{1-6} alkyl group), —SO_2NH_2, —$CONH_2$, —CN, -alkyl (e.g. —C_{1-6} alkyl, —CF_3), —SH, —S-alkyl (e.g. —S—C_{1-6} alkyl).

[0038] Most preferably at group Ar^1, Ar^2, Ar^3, Ar^4 and Ar^5, the expression "optionally substituted" refers to groups that are optionally substituted by one, two or three groups independently selected from F, Cl, hydroxy groups, groups of formula —O—C_{1-6} alkyl (especially —O—C_{1-4} alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), and —C_{1-6}alkyl (e.g. —C_{1-4}alkyl such as —CH_3 or —CF_3).

[0039] Especially preferably at group Ar^6, the expression "optionally substituted" refers to groups that are optionally substituted by one, two or three groups independently selected from halogen atoms, hydroxy groups, groups of formula —O-alkyl (e.g. —O—C_{1-6} alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), —NH_2, —$NR^{5a}R^{6a}$ (wherein R^{5a} and R^{6a} independently from each other are a hydrogen atom or an alkyl group such as

a C_{1-6} alkyl group), —SO_2NH_2, —$CONH_2$, —CN, -alkyl (e.g. —C_{1-6} alkyl, —CF_3), —SH, —S-alkyl (e.g. —S—C_{1-6} alkyl) and NO_2.

[0040] Most preferably at group Ar^6, the expression "optionally substituted" refers to groups that are optionally substituted by one, two or three groups independently selected from F, Cl, hydroxy groups, —NH_2, —NO_2, groups of formula —O—C_{1-6} alkyl (especially —O—C_{1-4}alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), and —C_{1-6} alkyl (e.g. —C_{1-4} alkyl such as —CH_3 or —CF_3).

[0041] The term halogen refers to F, Cl, Br or I.

[0042] According to a preferred embodiment, all alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, aralkyl and heteroaralkyl groups described herein may independently of each other optionally be substituted.

[0043] When an aryl, heteroaryl, cycloalkyl, alkylcycloalkyl, heteroalkylcycloalkyl, heterocycloalkyl, aralkyl or heteroaralkyl group contains more than one ring, these rings may be bonded to each other via a single or double bond or these rings may be annulated.

[0044] Owing to their substitution, compounds of formula (I) may contain one or more centers of chirality. The present invention therefore includes both all pure enantiomers and all pure diastereoisomers and also mixtures thereof in any mixing ratio. The present invention moreover also includes all cis/trans-isomers of the compounds of the general formula (I) and also mixtures thereof. The present invention moreover includes all tautomeric forms of the compounds of formula (I).

[0045] Preferably, when Ar^4 is absent, also L^3 is absent.

[0046] Further preferably, when Ar^5 is absent, also L^4 is absent.

[0047] Preferably, Ar^1 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen.

[0048] Further preferably, Ar^1 is an optionally substituted 1,4-phenylene group.

[0049] Preferably, Ar^2 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen.

[0050] Further preferably, Ar^2 is an optionally substituted 1,4-phenylene group.

[0051] Preferably, Ar^3 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen.

[0052] Further preferably, Ar^3 is an optionally substituted 1,4-phenylene group.

[0053] Preferably, Ar^4 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen.

[0054] Further preferably, Ar^4 is an optionally substituted 1,4-phenylene group.

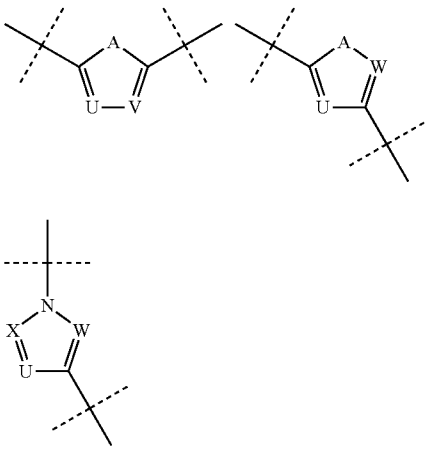
[0055] Preferably, Ar^5 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen.

[0056] Further preferably, Ar^5 is an optionally substituted 1,4-phenylene group.

[0057] Further preferably, Ar^4 is absent.

[0058] Further preferably, Ar^5 is absent.

[0059] The term 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen especially preferably refers to one of the following groups:



wherein A is 0, S or NH; U is N or CH; V is N or CH; W is N or CH; and X is N or CH.

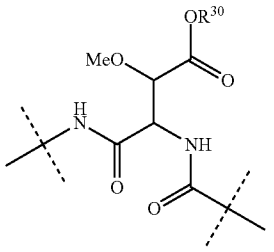
[0060] Further preferably, L^1 is a group of formula —CONH—, —NHCO—, —SO_2NH—, —$NHSO_2$—, —CH═CH—, —CR^3═CR^4— or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group.

[0061] Further preferably, L^2 is a group of formula —CONH—, —NHCO—, —SO_2NH—, —$NHSO_2$—, —CH═CH—, —CR^3═CR^4— or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group.

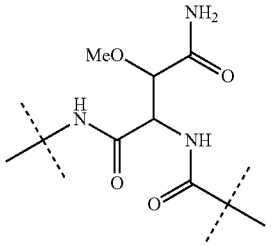
[0062] Further preferably, L^3 is absent or a group of formula —CONH—, —NHCO—, —SO_2NH—, —$NHSO_2$—, —CH═CH—, —CR^3═CR^4— or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group.

[0063] Further preferably, L^4 is absent or a group of formula —CONH—, —NHCO—, —SO_2NH—, —$NHSO_2$—, —CH═CH—, —CR^3═CR^4— or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group.

[0064] Further preferably, L^1 is NHCO (wherein the nitrogen atom is bound to Ar^1) or a group of the following formula:



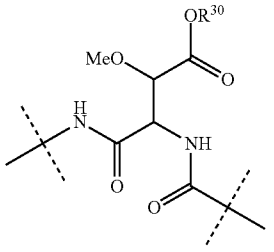
or



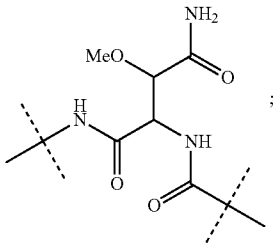
(wherein the NH group is bound to Ar^1), wherein R^{30} is a hydrogen atom or a C_{1-3} alkyl group.

[0065] Especially preferably, L^1 is NHCO (wherein the nitrogen atom is bound to Ar^1).

[0066] Moreover preferably, L^2 is NHCO (wherein the nitrogen atom is bound to Ar^2) or a group of the following formula:



or

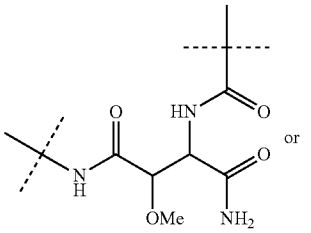


;

(wherein the NH group is bound to Ar^2), wherein R^{30} is a hydrogen atom or a C_{1-3} alkyl group.

[0067] Especially preferably, L^2 is NHCO (wherein the nitrogen atom is bound to Ar^1).

[0068] Further preferably, L^3 is absent or a group of the following formula:



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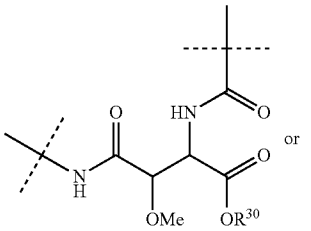
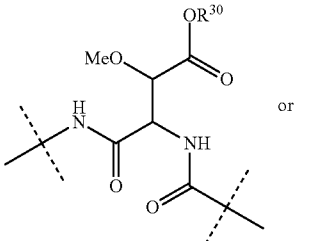
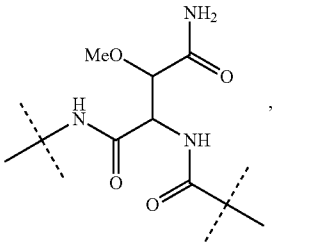


or



or



,

(wherein the NH group is bound to Ar^3), wherein R^{30} is a hydrogen atom or a C_{1-3}alkyl group.

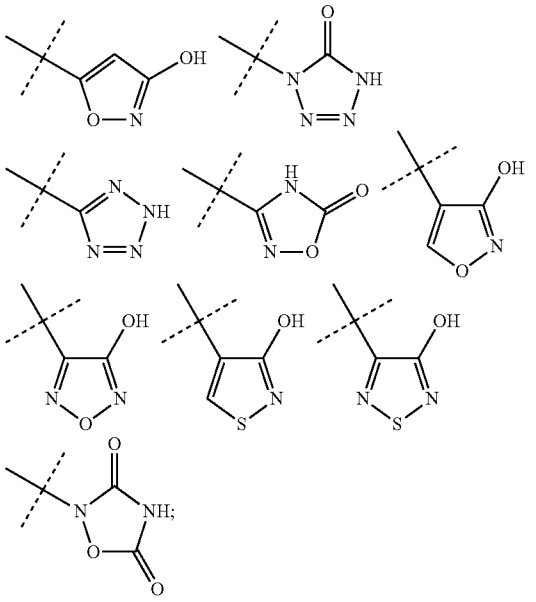
[0069] Further preferably, L^4 is absent or NHCO (wherein the nitrogen atom is bound to Ar^4).

[0070] Moreover preferably, R^{30} is a hydrogen atom.

[0071] Further preferably, R^1 is a hydrogen atom, a halogen atom or a group of formula —OH, —NH_2, —COOH, —SO_2NH_2, —$CONH_2$, —NO_2, —CN, -alkyl (e.g. —CF_3), —O-alkyl, —O—CO-alkyl, —NH-alkyl, —NH—CO-alkyl, or an optionally substituted heteroaryl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen, or an optionally substituted heterocycloalkyl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen.

[0072] Moreover preferably, R^2 is a hydrogen atom, a halogen atom or a group of formula —OH, —NH_2, —COOH, —SO_2NH_2, —$CONH_2$, —NO_2, —CN, -alkyl (e.g. —CF_3), —O-alkyl, —O—CO-alkyl, —NH-alkyl, —NH—CO-alkyl, or an optionally substituted heteroaryl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen, or an optionally substituted heterocycloalkyl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen.

[0073] Preferred examples of optionally substituted heteroaryl groups having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen and of optionally substituted heterocycloalkyl groups having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen as groups R^1 and R^2 are isosteres of carboxylic acid such as groups of the following formulas:



all these groups may optionally be further substituted.

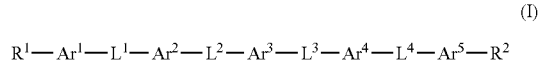
[0074] Especially preferably, R^1 is a group of formula $—NH_2$, $—NO_2$, $COOR^{11}$, or $—CONR^{12}R^{13}$; wherein R^{11}, R^{12} and R^{13} are independently a hydrogen atom or a C_{1-6} alkyl group; moreover preferably, R^1 is a group of formula —COOH.

[0075] Further especially preferably, R^2 is a group of formula $—NH_2$, $—NO_2$, $COOR^{11a}$, or $—CONR^{12a}R^{13a}$; wherein R^{11a}, R^{12a} and R^{13a} are independently a hydrogen atom or a C_{1-6} alkyl group; moreover preferably, R^2 is a group of formula $—NH_2$ or $—NO_2$.

[0076] Further especially preferably, R^1 is a heteroaryl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen, and which is substituted by a hydroxy group.

[0077] Further especially preferably, R^2 is a heteroaryl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen, and which is substituted by a hydroxy group.

[0078] Especially preferred are compounds of formula (I)



(I)

wherein

[0079] Ar^1 is an optionally substituted 1,4-phenylene group;

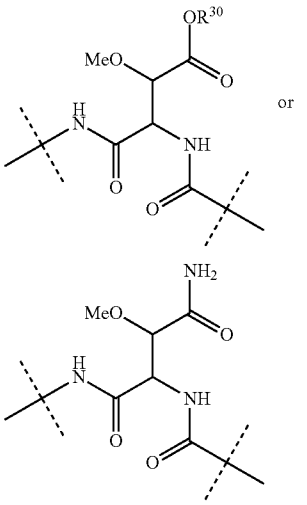
[0080] Ar^2 is an optionally substituted 1,4-phenylene group;

[0081] Ar^3 is an optionally substituted 1,4-phenylene group;

[0082] Ar^4 is absent or an optionally substituted 1,4-phenylene group;

[0083] Ar^5 is absent or an optionally substituted 1,4-phenylene group;

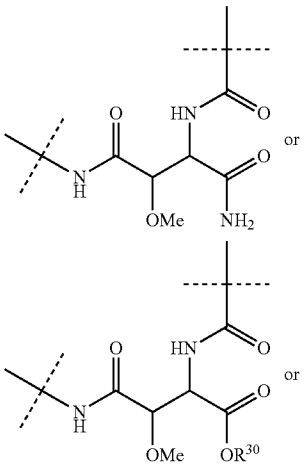
[0084] L^1 is a group of formula —CONH—, —NHCO—, $—SO_2NH—$ or $—NHSO_2—$ or a group of the following formula:



(wherein the NH group is bound to Ar^1);

[0085] L^2 is a group of formula —CONH—, —NHCO—, $—SO_2NH—$ or $—NHSO_2—$;

[0086] L^3 is absent or a group of formula —CONH—, —NHCO—, $—SO_2NH—$ or $—NHSO_2—$ or a group of the following formula:



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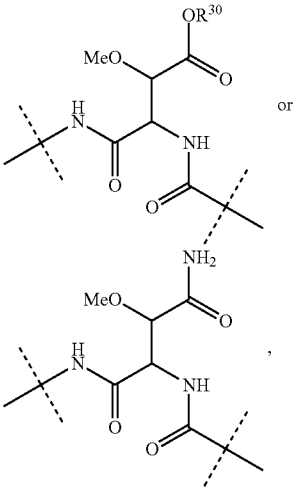


(wherein the NH group is bound to Ar^3);

[0087] L^4 is absent or a group of formula —CONH—, —NHCO—, —SO_2NH— or —NHSO_2—;

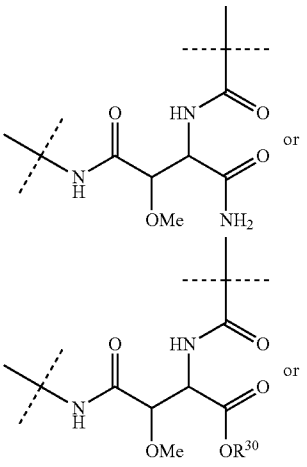
[0088] R^{30} is a hydrogen atom or a C_{1-3} alkyl group (especially preferably, a hydrogen atom);

[0089] R^1 is a group of formula —NH_2, —NO_2, $COOR^{11}$, or —$CONR^{12}R^{11}$; wherein R^{11}, R^{12} and R^{13} are independently a hydrogen atom or a C_{1-6} alkyl group (especially preferably, R^1 is a group of formula —COOH); and

[0090] R^2 is a group of formula —NH_2, —NO_2, $COOR^{11a}$, or —$CONR^{12a}R^{13a}$; wherein R^{11a}, R^{12a} and R^{13a} are independently a hydrogen atom or a C_{1-6} alkyl group (especially preferably, R^2 is a group of formula —NH_2 or —NO_2);

[0091] or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

[0092] Therein, preferably, L^1 is a group of formula —CONH—, —NHCO—, —SO_2NH— or —NHSO_2—, and L^3 is absent or a group of the following formula:



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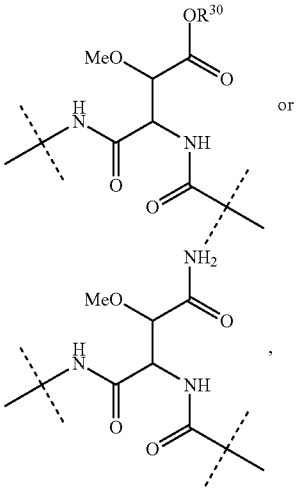
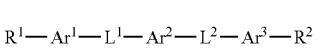


(wherein the NH group is bound to Ar^3).

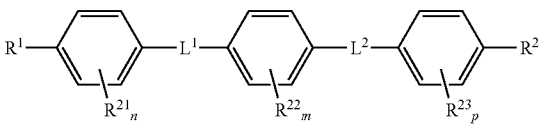
[0093] Further preferred are compounds of formula (II)



(II)

wherein Ar^1, Ar^2, Ar^3, L^1, L^2, R^1 and R^2 are as defined above.

[0094] Moreover preferred are compounds of formula (III)



(III)

wherein

[0095] n is 0, 1, 2, 3 or 4;

[0096] m is 0, 1, 2, 3 or 4;

[0097] p is 0, 1, 2, 3 or 4;

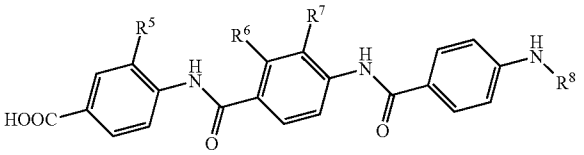
group(s) R^{21} are independently selected from halogen atoms, hydroxy groups, groups of formula —O-alkyl (e.g. —O—C_{1-6}alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), —NH_2, —$NR^{5a}R^{6a}$ (wherein R^{5a} and R^{6a} independently from each other are a hydrogen atom or an alkyl group such as a C_{1-6} alkyl group), —SO_2NH_2, —$CONH_2$, —CN, -alkyl (e.g. —C_{1-6}alkyl, —CF_3), —SH, —S-alkyl (e.g. —S—C_{1-6}alkyl); group(s) R^{22} are independently selected from halogen atoms, hydroxy groups, groups of formula —O-alkyl (e.g. —O—C_{1-6}alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), —NH_2, —$NR^{5a}R^{6a}$ (wherein R^{5a} and R^{6a} independently from each other are a hydrogen atom or an alkyl group such as a C_{1-6} alkyl group), —SO_2NH_2, —$CONH_2$, —CN, -alkyl (e.g. —C_{1-6}alkyl, —CF_3), —SH, —S-alkyl (e.g. —S—C_{1-6} alkyl); group(s) R^{23} are independently selected from halogen atoms, hydroxy groups, groups of formula —O-alkyl (e.g. —O—C_{1-6}alkyl such as —OMe, —OEt, —O-nPr, —O-iPr, —O-nBu, —O-iBu or —O-tBu), —NH_2, —$NR^{5a}R^{6a}$ (wherein R^{5a} and R^{6a} independently from each other are a hydrogen atom or an alkyl group such as a C_{1-6} alkyl group),

—SO_2NH_2, —$CONH_2$, —CN, -alkyl (e.g. —C_{1-6}alkyl, —CF_3), —SH, —S-alkyl (e.g. —S—C_{1-6} alkyl); and

[0098] R^1, R^2, L^1 and L^2 are as defined above.

[0099] Further preferred are compounds of formula (IV)

(IV)



wherein

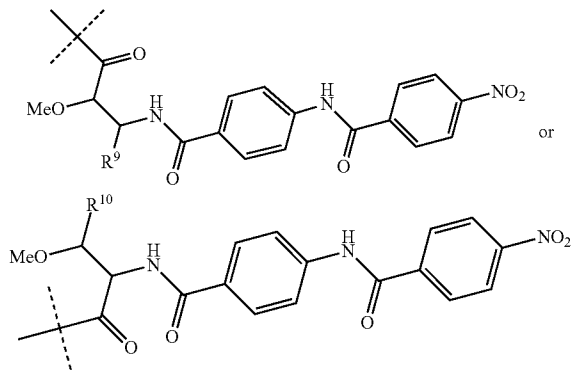
[0100] R^5 is a group of formula —O—C_{1-6}alkyl;

[0101] R^6 is a hydroxy group;

[0102] R^7 is a group of formula —O—C_{1-6}alkyl; and

[0103] R^8 is a hydrogen atom, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group.

[0104] Preferably, R^8 is a hydrogen atom or a group of the following formula:

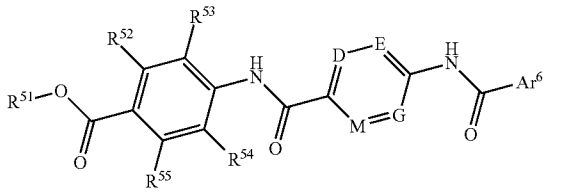


wherein R^9 is COOH or $CONH_2$ and R^{10} is COOH or $CONH_2$.

[0105] Moreover preferably, R^5 is a group of formula —O—C_{1-4} alkyl and R^7 is a group of formula —O—C_{1-4} alkyl.

[0106] Further preferred are compounds of formula (V)

(V)



wherein

[0107] R^{51} is a hydrogen atom, or a C_{1-6} alkyl group;

[0108] R^{52} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0109] R^{53} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0110] R^{54} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6}alkyl;

[0111] R^{55} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0112] D is N or CR^{56};

[0113] E is N or CR^{57};

[0114] G is N or CR^{58};

[0115] M is N or CR^{59};

[0116] R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0117] R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0118] R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6}alkyl;

[0119] R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl; and

[0120] Ar^6 is an optionally substituted (by one, two or more substituents such as e.g. R^2, R^8 or NHR^8) phenyl group or an optionally substituted (by one, two or more substituents such as e.g. R^2, R^8 or NHR^8) heteroaryl group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0121] or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

[0122] Especially preferred are compounds of Formula (V) wherein:

[0123] R^{51} is a hydrogen atom, or a C_{1-4} alkyl group;

[0124] R^{52} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

[0125] R^{53} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4}alkyl;

[0126] R^{54} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

[0127] R^{55} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

[0128] D is N or CR^{56};

[0129] E is N or CR^{57};

[0130] G is N or CR^{58};

[0131] M is N or CR^{56};

[0132] R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

[0133] R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

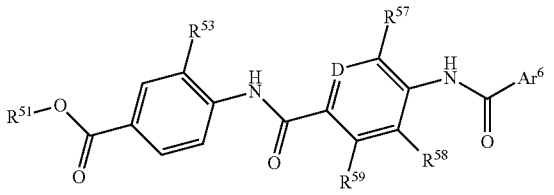
[0134] R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl; and

[0135] R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-4} alkyl.

[0136] Especially preferably, only one or two (especially only one) of D, E, G and M is/are N.

[0137] Further preferred are compounds of formula (VI)

(VI)



wherein

[0138] R^{51} is a hydrogen atom, or a C_{1-6} alkyl group;

[0139] R^{53} is F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl (especially preferably a group of formula —O—C_{1-6} alkyl);

[0140] D is N or CR^{56};

[0141] R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0142] R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0143] R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0144] R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6}alkyl; and

[0145] Ar^6 is an optionally substituted (by one, two or more substituents such as e.g. R^2, R^8 or NHR^8) phenyl group or an optionally substituted (by one, two or more substituents such as e.g. R^2, R^8 or NHR^8) heteroaryl group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

[0146] or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

[0147] Especially preferred are compounds of Formula (VI) wherein:

[0148] R^{51} is a hydrogen atom, or a C_{1-4} alkyl group;

[0149] R^{53} is F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl (especially preferably a group of formula —O—C_{1-4} alkyl);

[0150] D is N or CR^{58};

[0151] R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

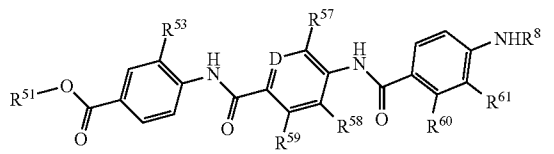
[0152] R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4}alkyl;

[0153] R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl; and

[0154] R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl.

[0155] Further preferred are compounds of formula (VII)

(VII)



wherein

[0156] R^{51} is a hydrogen atom, or a C_{1-6} alkyl group;

[0157] R^{53} is F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl (especially preferably a group of formula —O—C_{1-6} alkyl);

[0158] D is N or CR^{56};

[0159] R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0160] R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6}alkyl;

[0161] R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0162] R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

[0163] R^{60} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6}alkyl;

[0164] R^{61} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6}alkyl; and

[0165] R^8 is a hydrogen atom, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group.

[0166] or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

[0167] Especially preferred are compounds of Formula (VII) wherein:

[0168] R^{51} is a hydrogen atom, or a C_{1-4} alkyl group;

[0169] R^{53} is F, Cl, a hydroxy group, a C_{1-4}alkyl group or a group of formula —O—C_{1-4} alkyl (especially preferably a group of formula —O—C_{1-4} alkyl);

[0170] D is N or CR^{66};

[0171] R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4}alkyl;

[0172] R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4}alkyl;

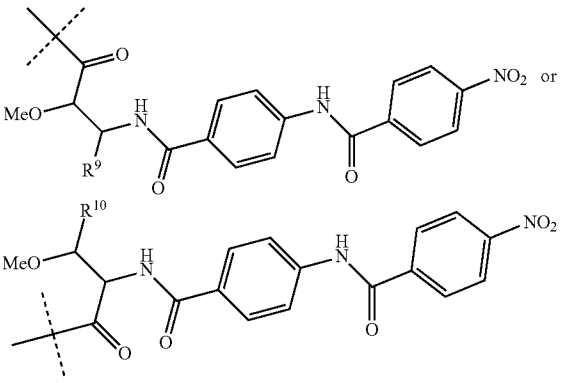
[0173] R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

[0174] R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl;

[0175] R^{60} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl; and

[0176] R^{61} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-4} alkyl group or a group of formula —O—C_{1-4} alkyl.

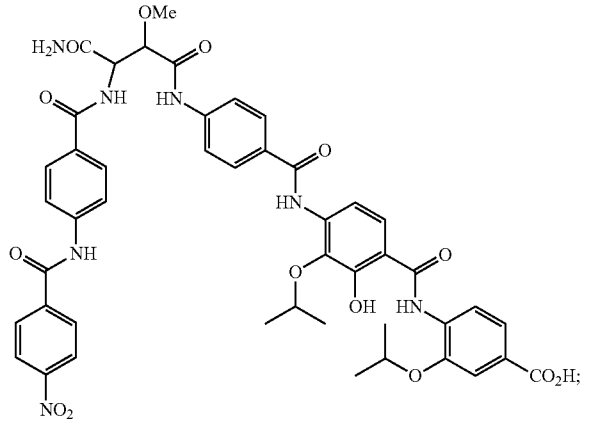
[0177] Preferably, R^8 is a hydrogen atom or a group of the following formula:



wherein R^9 is COOH or $CONH_2$ and R^{10} is COOH or $CONH_2$.

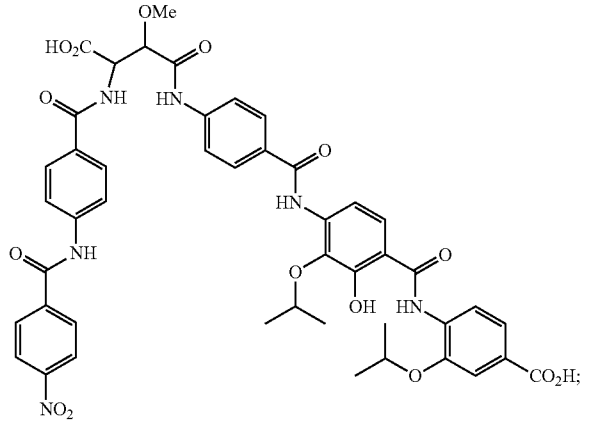
[0178] Especially preferred are the following compounds:

(1)



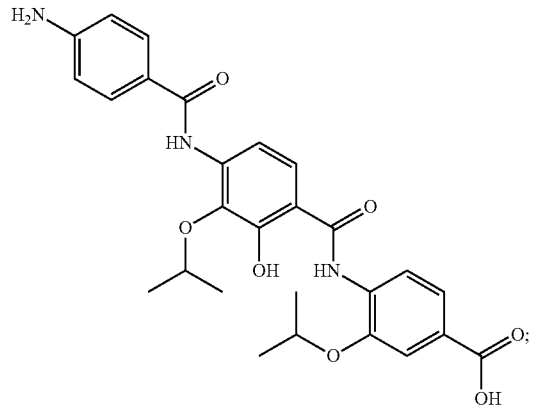
Cystobactamide A

(2)



Cystobactamide B

(3)



Cystobactamide C

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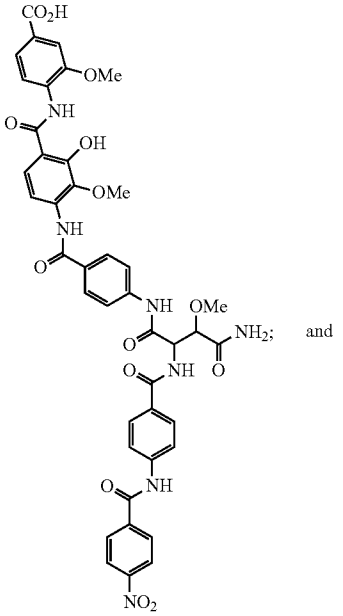
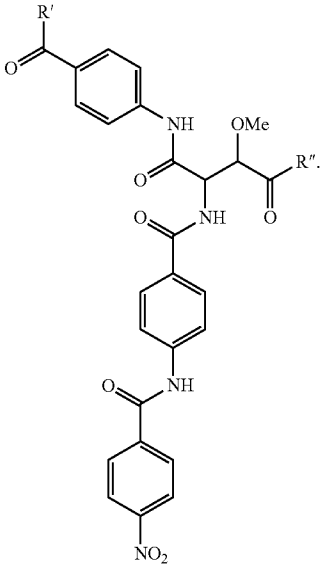
(4)



Cystobactamide D

(5)

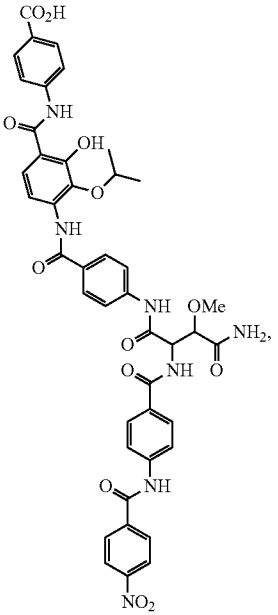


Cystobactamide E

(R' is NH_2 or OH and R'' is NH_2 or OH)

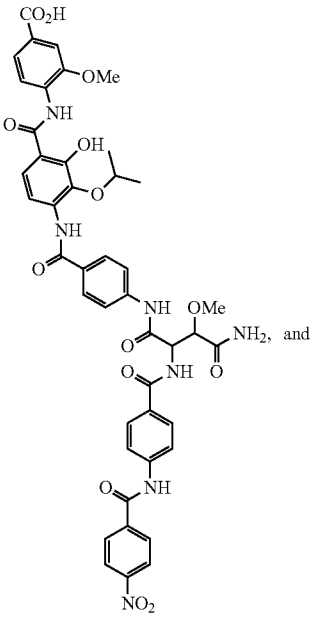
[0179] Moreover especially preferred are the following compounds:

(6)



Cystobactamide F

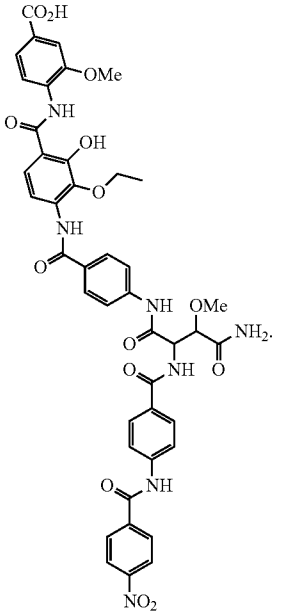
(7)



Cystobactamide G

-continued

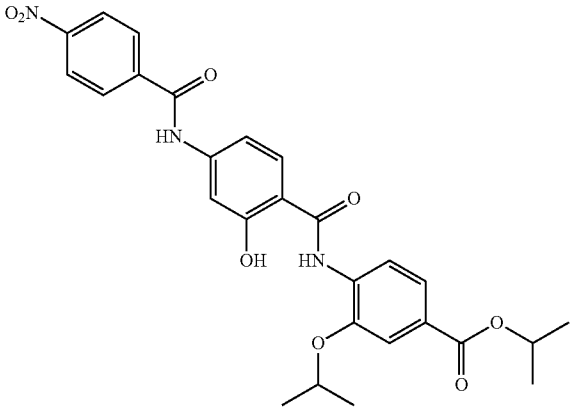
(8)



Cystobactamide H

[0180] Moreover preferred are the following compounds:

(1a)



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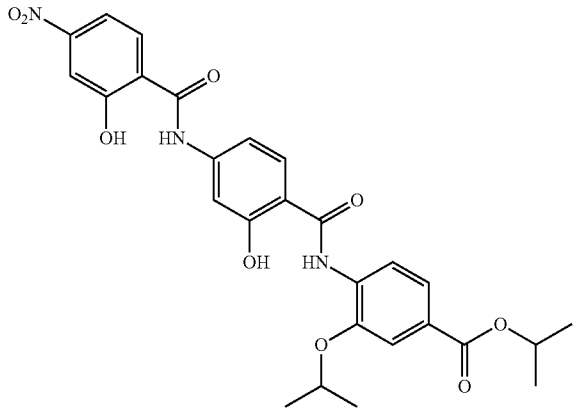
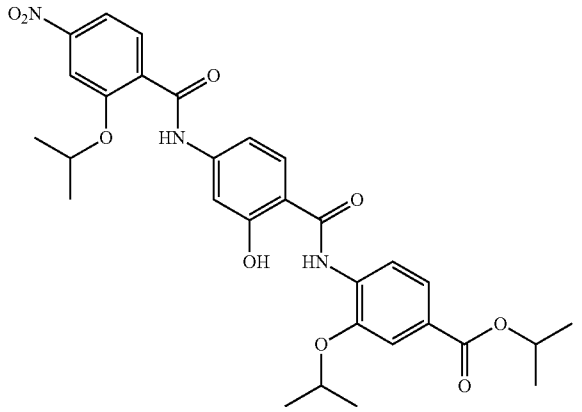
(2a)



(3a)



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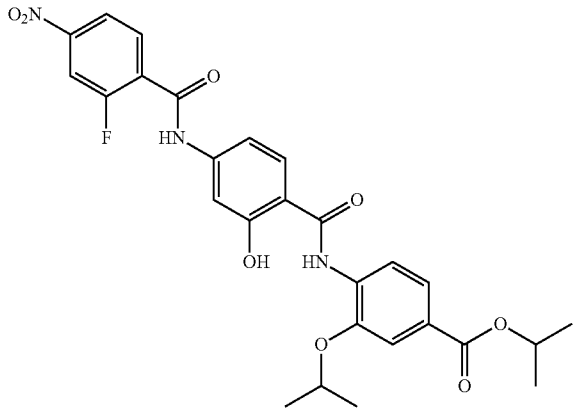

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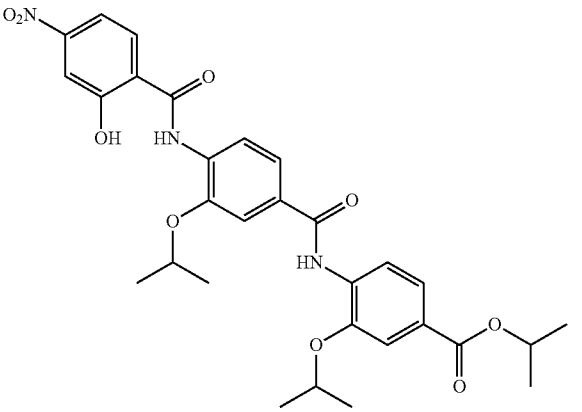

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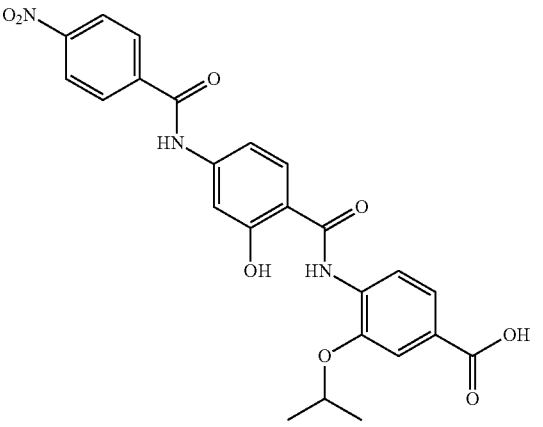

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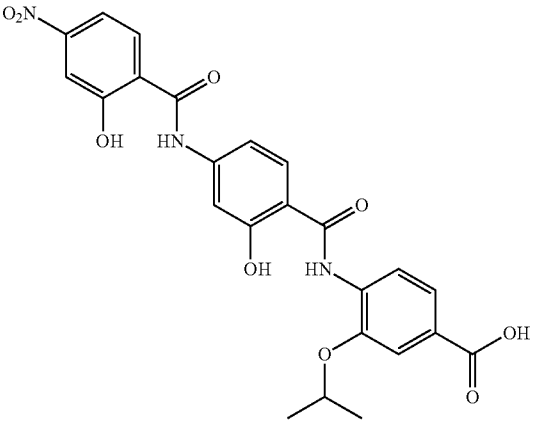

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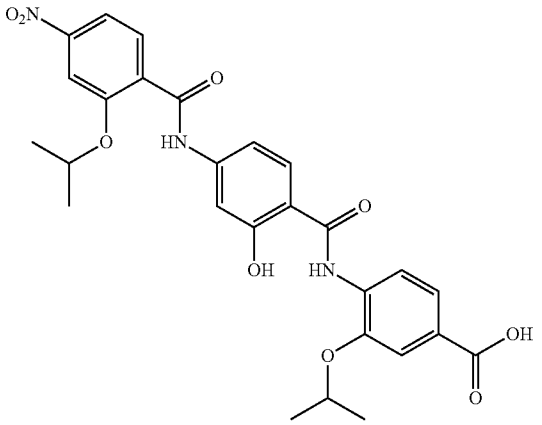

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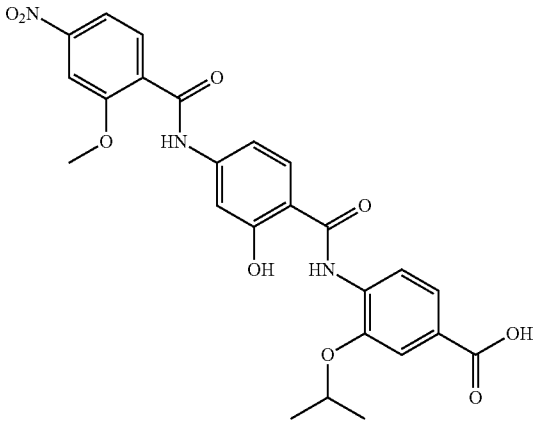

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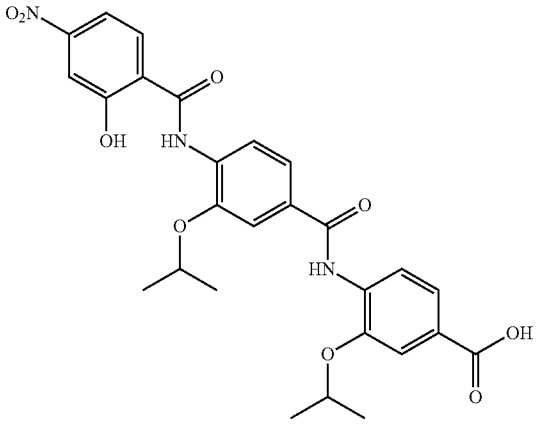

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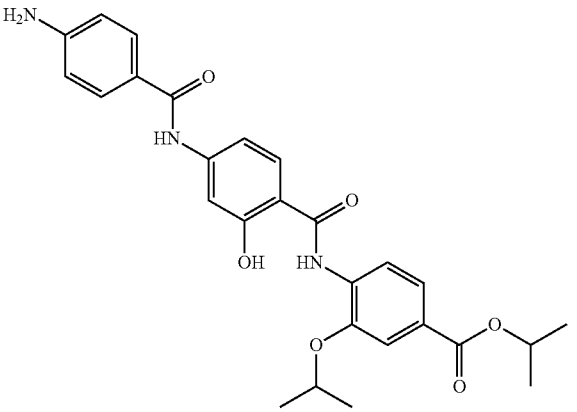

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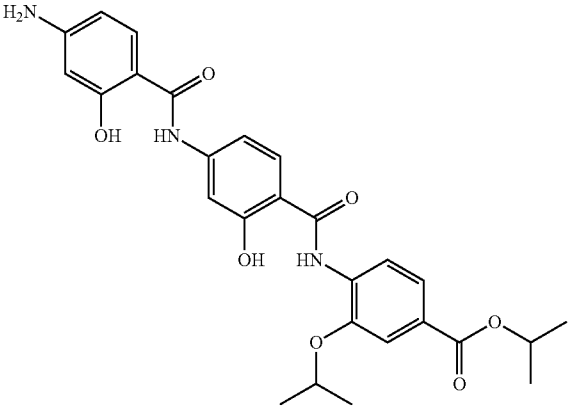

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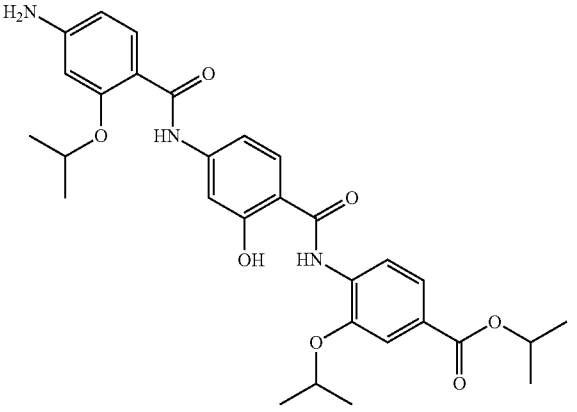

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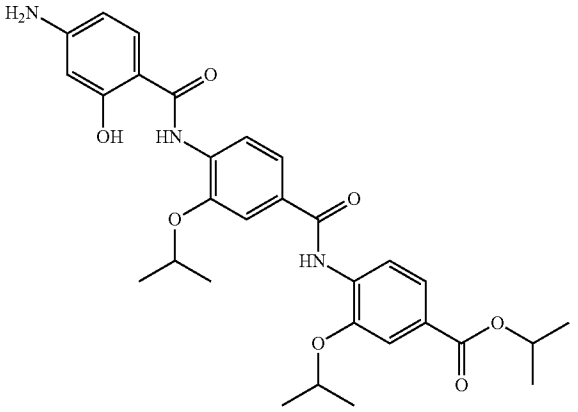

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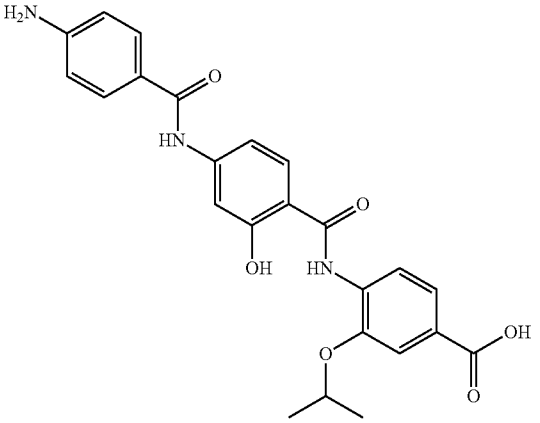

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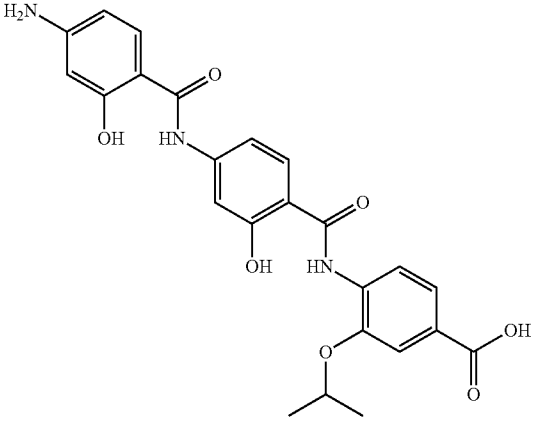

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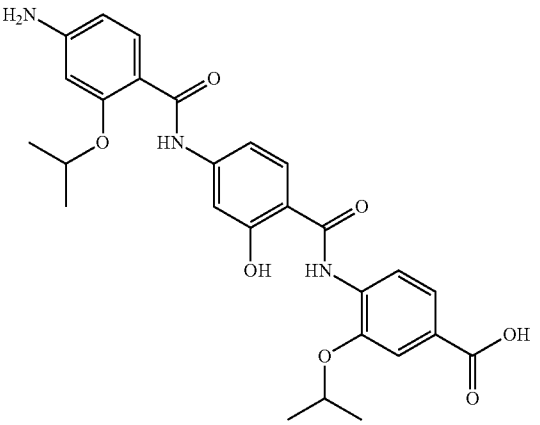

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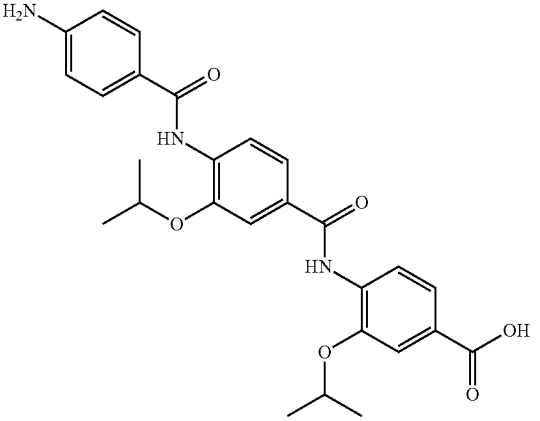

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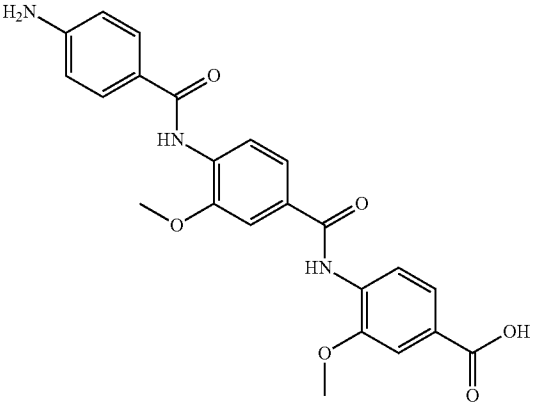

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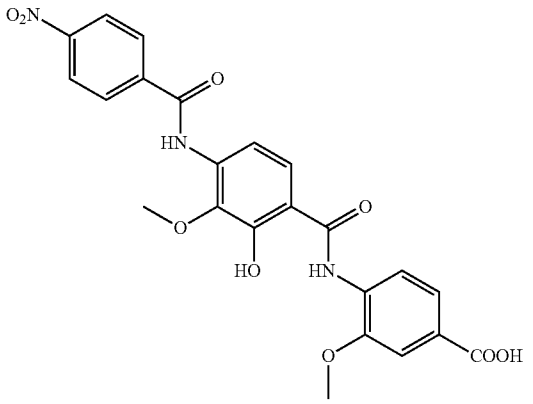

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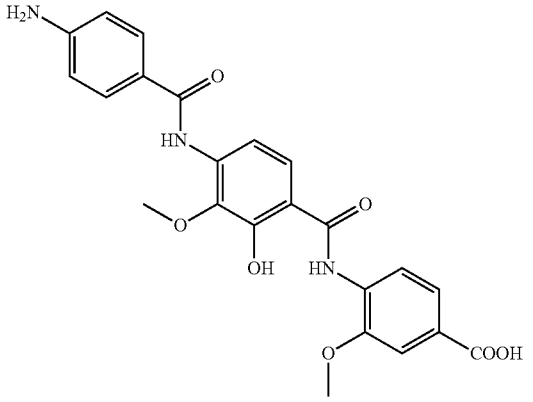

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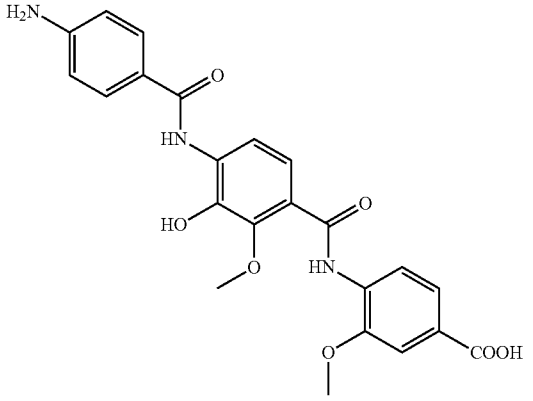

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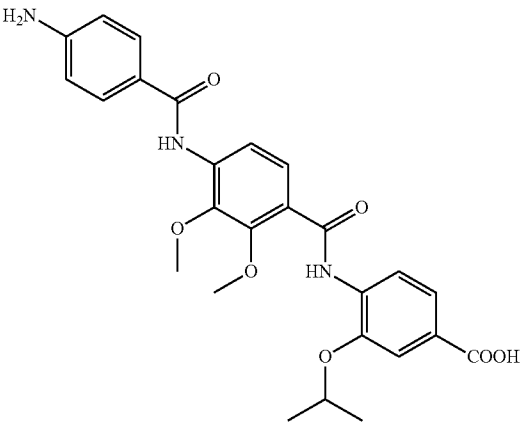

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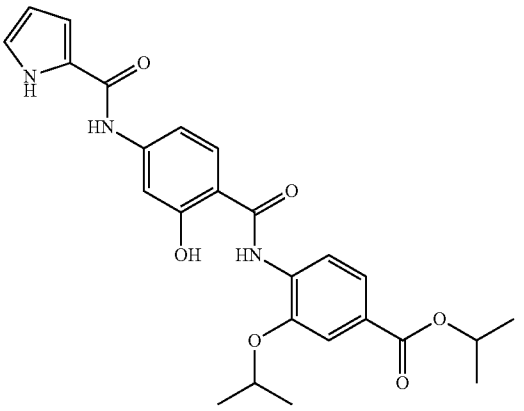

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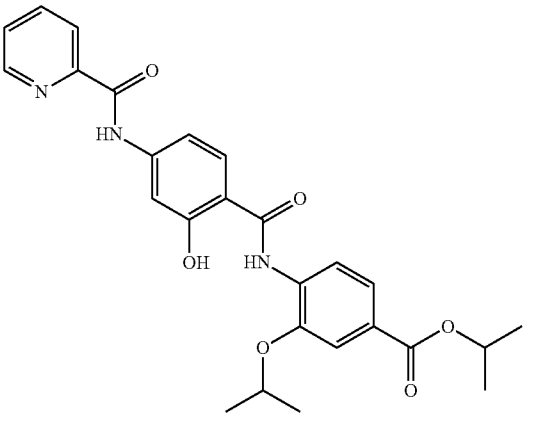

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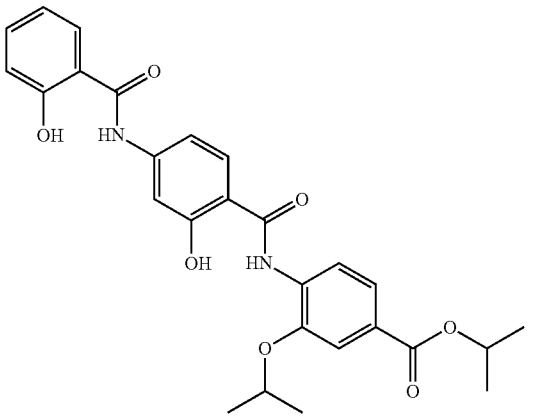

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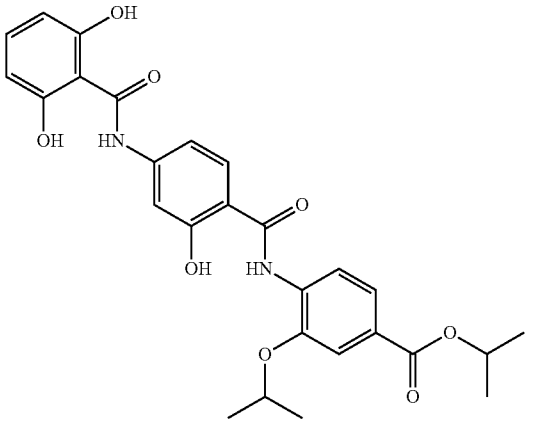

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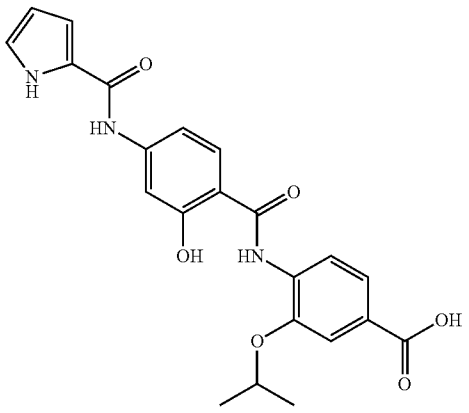

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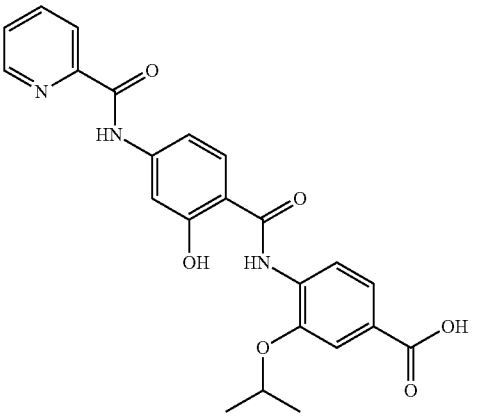

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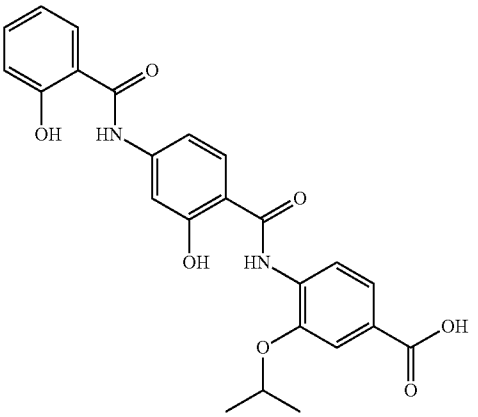

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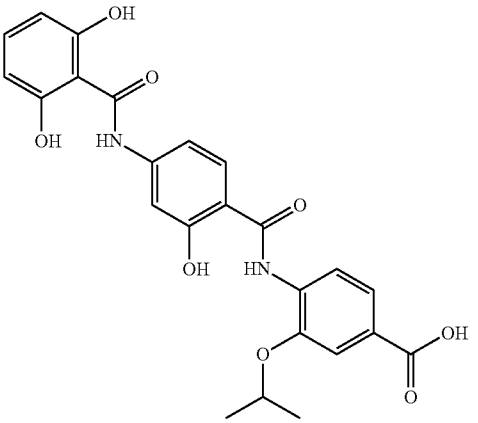

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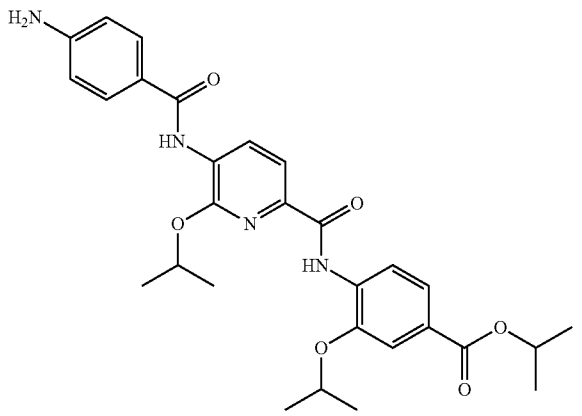

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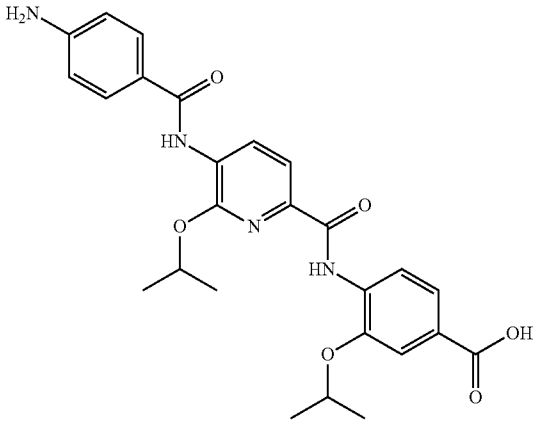


[0181] The present invention further provides pharmaceutical compositions comprising one or more compounds described herein or a pharmaceutically acceptable salt, solvate or hydrate thereof, optionally in combination with one or more carrier substances and/or one or more adjuvants.

[0182] The present invention furthermore provides compounds or pharmaceutical compositions as described herein for use in the treatment and/or prophylaxis of bacterial infections, especially caused by *E. coli, P. aeruginosa, A. baumannii*, other Gram-negative bacteria, and Gram-positive bacteria.

[0183] Moreover preferably, the present invention provides compounds for use in the treatment and/or prophylaxis of bacterial infections, especially caused by *Pseudomonas aeruginosa* and other Gram-negative bacteria.

[0184] It is a further object of the present invention to provide a compound as described herein or a pharmaceutical composition as defined herein for the preparation of a medicament for the treatment and/or prophylaxis of bacterial infections, especially caused by selected Gram-negative bacteria and Gram-positive bacteria.

[0185] Examples of pharmacologically acceptable salts of sufficiently basic compounds are salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleic and salicylic acid. Further, a sufficiently acidic compound may form alkali or earth alkali metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, meglumin, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts; all of which are also further examples of salts of the compounds described herein. The compounds described herein may be solvated, especially hydrated. The hydratization/hydration may occur during the process of production or as a consequence of the hygroscopic nature of the initially water free compounds. The solvates and/or hydrates may e.g. be present in solid or liquid form.

[0186] The therapeutic use of the compounds described herein, their pharmacologically acceptable salts, solvates and hydrates, respectively, as well as formulations and pharmaceutical compositions also lie within the scope of the present invention.

[0187] The pharmaceutical compositions according to the present invention comprise at least one compound described herein and, optionally, one or more carrier substances and/or adjuvants.

[0188] As mentioned above, therapeutically useful agents that contain compounds described herein, their solvates, salts or formulations are also comprised in the scope of the present invention. In general, the compounds described herein will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent.

[0189] For oral administration such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragees, coated tablets, pills, semisolids, soft or hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystals or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containing the active ingredient or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard, e.g. gelatine, capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients as are e.g. lactose, sucrose, glucose, gelatine, malt, silica gel, starch or derivatives thereof, talc, stearinic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat, and polyols. For the production of liquid solutions, emulsions or suspensions or syrups one may use as excipients e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, lipids, phospholipids, cyclodextrins, vegetable, petroleum, animal or synthetic oils. Especially preferred are lipids and more preferred are phospholipids (preferred of natural origin; especially preferred with a particle size between 300 to 350 nm) preferred in phosphate buffered saline (pH=7 to 8, preferred 7.4). For suppositories one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as are e.g. oxygen, nitrogen and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabiliza-

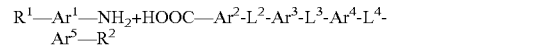
tion, e.g. UV stabilizers, emulsifiers, sweetener, aromatizers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

[0190] In general, in the case of oral or parenteral administration to adult humans weighing approximately 80 kg, a daily dosage of about 1 mg to about 10,000 mg, preferably from about 5 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion or subcutaneous injection.

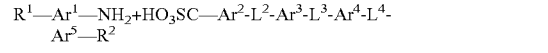
[0191] The compounds of the present invention can be prepared by fermentation (e.g. by fermentation of strain MCy8071 DSM27004) or by chemical synthesis applying procedures known to a person skilled in the art.

[0192] For example the compounds of the present invention can be prepared according to the following procedures:

[0193] Starting from the respective optionally substituted building blocks (e.g. Ar^1, Ar^2, Ar^3, Ar^4 and Ar^5), these building blocks can be linked to each other using acid chlorides or coupling reagents which are known to a person skilled in the art, e.g. according to the following reaction scheme:

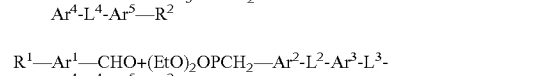


$$R^1—Ar^1—NH_2+HOOC—Ar^2\text{-}L^2\text{-}Ar^3\text{-}L^3\text{-}Ar^4\text{-}L^4\text{-}Ar^5—R^2$$

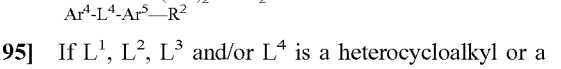


$$R^1—Ar^1—NH_2+HO_3SC—Ar^2\text{-}L^2\text{-}Ar^3\text{-}L^3\text{-}Ar^4\text{-}L^4\text{-}Ar^5—R^2$$

[0194] If L^1, L^2, L^3 and/or L^4 is a group of formula —CH═CH— (or another olefine group), the respective optionally substituted building blocks (e.g. Ar^1, Ar^2, Ar^3, Ar^4 and Ar^5) can be linked to each other using a Wittig or a Homer reaction, e.g. according to the following reaction scheme:



$$R^1—Ar^1—CHO+BrPh_3P—CH_2—Ar^2\text{-}L^2\text{-}Ar^3\text{-}L^3\text{-}Ar^4\text{-}L^4\text{-}Ar^5—R^2$$



$$R^1—Ar^1—CHO+(EtO)_2OPCH_2—Ar^2\text{-}L^2\text{-}Ar^3\text{-}L^3\text{-}Ar^4\text{-}L^4\text{-}Ar^5—R^2$$

[0195] If L^1, L^2, L^3 and/or L^4 is a heterocycloalkyl or a heteroaryl group, the respective optionally substituted building blocks (e.g. Ar^1, Ar^2, Ar^3, Ar^4 and Ar^5) can be linked to each other applying similar reaction conditions.

[0196] Identification of the cystobactamide biosynthesis gene cluster:

[0197] The genome of the cystobactamid producer has been sequenced by shotgun-sequencing. As the main building block of the cystobactamides is the non-proteinogenic amino acid p-aminobenzoic acid (PABA), p-aminobenzoic acid synthase (query, NP_415614) was used as query for the identification of a putative cystobactamide biosynthetic cluster in the genome of Cbv34. Importantly, a p-aminobenzoic acid synthase homologue could be identified (CysD, FIG. **12** and table A), which is forming an operon with non-ribosomal peptide synthases (CysG, H and K) in the context of an in silico predicted ~48 kb large NRPS cluster (FIG. **12**, assignment: table A). The genes in this NRPS cluster have been analysed by pfam, NCBI BLAST and phyre2. Aside the p-aminobenzoic acid synthase homologue, two further PABA biosynthetic enzymes can be found in the cluster: an aminodeoxychorismate lyase (CysI) and a 3-deoxy-d-arabino-heptulosonate-7-phosphate (DAHP) synthase (CysN). DAHP synthase (CysN) is a key enzyme for the production of shikimate and chorismate. In the main trunk of the shikimate pathway, D-erythrose 4-phosphate and phosphoenolpyruvate (DAHP synthase) are converted via shikimate to chorismate. CysI and CysD allow the direct biosynthesis of PABA from chorismate. Furthermore, the cluster contains a p-aminobenzoic acid N-oxygenase homologue (CysR).

[0198] FIG. **12** shows the cystobactamide biosynthetic cluster of the invention.

[0199] A recombinant biosynthesis cluster capable of synthesizing a cystobactamide selected from the group consisting of cystobactamide A, B, C, D, E, F, G and H, wherein the cluster comprises all of the polypeptides, or a functional variant thereof, according to SEQ ID NOs. 40 to 73.

[0200] The term "functional variant" as used herein denotes a polypeptide having a sequence that is at least 85%, 90%, 95% or 99% identical to a polypeptide sequence described herein. A "functional variant" of a polypeptide may retain amino acids residues recognized as conserved for the polypeptide in nature, and/or may have non-conserved amino acid residues. Amino acids can be, relative to the native polypeptide, substituted (different), inserted, or deleted, but the variant has generally similar (enzymatic) activity or function as compared to a polypeptide described herein. A "functional variant" may be found in nature or be an engineered mutant (recombinant) thereof.

[0201] The term "identity" refers to a property of sequences that measures their similarity or relationship. Identity is measured by dividing the number of identical residues by the total number of residues and multiplying the product by 100.

[0202] The terms "protein", "polypeptide", "peptide" as used herein define an organic compound made of two or more amino acid residues arranged in a linear chain, wherein the individual amino acids in the organic compound are linked by peptide bonds, i.e. an amide bond formed between adjacent amino acid residues. By convention, the primary structure of a protein is reported starting from the amino-terminal (N) end to the carboxyl-terminal (C) end.

[0203] As used herein, "comprising", "including", "containing", "characterized by", and grammatical equivalents thereof are inclusive or open-ended terms that do not exclude additional, unrecited elements or method steps. "Comprising", etc. is to be interpreted as including the more restrictive term "consisting of".

[0204] As used herein, "consisting of" excludes any element, step, or ingredient not specified in the claim.

[0205] When trade names are used herein, it is intended to independently include the trade name product formulation, the generic drug, and the active pharmaceutical ingredient(s) of the trade name product.

[0206] In general, unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs, and are consistent with general textbooks and dictionaries.

[0207] Preferably, the NRPS enzyme of the invention is a not naturally occurring NRPS. The NRPS of the invention may also be a hybrid NRPS comprising modules, domains, and/or portions thereof, or functional variants thereof, from two or more NRPSs or from one or more polyketide synthase (s) (PKSs).

[0208] The cystobactamide biosynthesis cluster of the invention preferably includes the elements of Table A.

TABLE A

Cystobactamide gene cluster of the invention. Gene and NRPS domain annotation with the gene cluster sequence corresponding to SEQ ID NO. 1.

	location within the gene cluster sequence (bp)					NRPS						
							location within the gene cluster sequence (bp)			location within the protein sequence (aa)		
Name	Min.	Max.	direction	Length	aa	Domains	length	Min.	Max.	length	Min.	Max.
Orf1	15	845	reverse	831	276							
Orf2	912	1148	reverse	237	78							
Orf3	1339	1827	reverse	489	162							
Orf4	1907	2170	reverse	264	87							
Orf5	2347	2796	reverse	450	149							
CysT	3035	6838	reverse	3804	1267							
CysS	7049	8977	reverse	1929	642							
CysR	9086	10087	reverse	1002	333							
CysQ	10162	10956	reverse	795	264							
CysP	11029	11730	reverse	702	233							
CysO	11764	12375	reverse	612	203							
CysA	12715	12927	forward	213	70							
CysB	12996	13949	forward	954	317							
CysC	13959	15338	forward	138	45							
CysD	15464	17662	forward	2199	732							
CysE	17749	18480	forward	732	243							
CysF	18503	19540	forward	1038	345							
CysG	19580	25558	forward	5979	1992	AMP-binding domain	1451	19694	21145	483	39	521
						PCP domain	209	21221	21430	69	548	616
						Condensation_LCL domain	893	21485	22378	297	636	932
						AMP-binding domain	1451	22880	24331	483	1101	1583
						PCP domain	215	24404	24619	71	1609	1679
						Thioesterase domain	788	24728	25516	262	1717	1978
CysH	25626	28553	forward	2928	975	AMP-binding domain	1199	25737	26936	399	38	436
						novel domain type	332	27231	27563	110	536	645
						AMP binding domain C-terminus	170	28032	28202	56	803	858
						PCP domain	197	28284	28481	65	887	951
CysI	28555	29373	forward	819	272							
CysJ	29392	30375	forward	984	327							
CysK	30450	44087	forward	13638	4545	Condensation_LCL domain	323	30459	30782	107	4	110
						AMP-binding domain	1505	31239	32744	501	264	764
						PCP domain	197	32820	33017	65	791	855
						Condensation_LCL domain	893	33072	33965	297	875	1171
						AMP-binding domain	1505	34461	35966	501	1338	1838
						PCP domain	197	36042	36239	65	1865	1929
						Condensation_LCL domain	890	36285	37175	296	1946	2241
						AMP-binding domain	1574	37668	39242	524	2407	2930
						PCP domain	359	39165	39524	119	2906	3024
						Condensation_LCL domain	893	39579	40472	297	3044	3340
						AMP-binding domain	1505	40968	42473	501	3507	4007
						PCP domain	197	42549	42746	65	4034	4098
						Condensation_LCL domain	896	42801	43697	298	4118	4415
CysL	44084	47155	forward	3072	1023	AMP-binding domain	1445	45665	47110	481	528	1008
CysM	47152	47268	forward	117	38							
CysN	47280	48353	forward	1074	357							
Orf6	48490	50067	reverse	1578	525							
Orf7	50064	50849	reverse	786	261							
Orf8	50855	52156	reverse	1302	433							

TABLE A-continued

Cystobactamide gene cluster of the invention. Gene and NRPS domain annotation with the gene cluster sequence corresponding to SEQ ID NO. 1.

location within the gene cluster sequence (bp)							NRPS					
							location within the gene cluster sequence (bp)			location within the protein sequence (aa)		
Name	Min.	Max.	direction	Length	aa	Domains	length	Min.	Max.	length	Min.	Max.
Orf9	52161	54266	reverse	2106	701							
Orf10	54266	55027	reverse	762	253							
Orf11	55486	56679	forward	1194	397							
Orf12	56760	57134	forward	375	124							
Orf13	57166	57504	reverse	339	112							
Orf14	57504	58418	reverse	915	304							

[0209] The present invention also provides isolated, synthetic or recombinant nucleic acids that encode NRPSs of the invention. Said nucleic acids include nucleic acids that include a portion or all of a NRPS of the invention, nucleic acids that further include regulatory sequences, such as promoter and translation initiation and termination sequences, and can further include sequences that facilitate stable maintenance in a host cell, i.e., sequences that provide the function of an origin of replication or facilitate integration into host cell chromosomal or other DNA by homologous recombination. These NRPSs may be used as research tools or as modules in recombinant NRPS or PKS clusters.

[0210] Preferably, the invention relates to an isolated, synthetic or recombinant nucleic acid comprising:

[0211] (i) a sequence encoding a cystobactamide biosynthesis cluster, wherein the sequence has a sequence identity to the full-length sequence of SEQ ID NO. 1 from at least 85%, 90%, 95%, 96%, 97%, 98%, 98.5%, 99%, or 99.5% to 100%;

[0212] (ii) a sequence encoding a NRPS, wherein the sequence has a sequence identity to the full-length sequence of any of SEQ ID NOs. 8, 9, 12 or 13 from at least 85%, 90%, 95%, 96%, 97%, 98%, 98.5%, 99%, or 99.5% to 100%;

[0213] (iii) a sequence completely complementary to the full length sequence of any nucleic acid sequence of (i) or (ii); or

[0214] (iv) a sequence encoding a polypeptide according to any of SEQ ID NOs. 46, 47, 50 or 51.

[0215] The phrases "nucleic acid" or "nucleic acid sequence" as used herein refer to an oligonucleotide, nucleotide, polynucleotide, or to a fragment of any of these, to DNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent a sense or antisense strand, natural or synthetic in origin. "Oligonucleotide" includes either a single stranded polydeoxynucleotide or two complementary polydeoxynucleotide strands that may be chemically synthesized. Such synthetic oligonucleotides have no 5' phosphate and thus will not ligate to another oligonucleotide without adding a phosphate with an ATP in the presence of a kinase. A synthetic oligonucleotide can ligate to a fragment that has not been dephosphorylated. A "coding sequence" of or a "nucleotide sequence encoding" a particular polypeptide or protein, is a nucleic acid sequence which is transcribed and translated into a polypeptide or protein when placed under the control of appropriate regulatory sequences. The nucleic acids used to practice this invention may be isolated from a variety of sources, genetically engineered, amplified, and/or expressed/generated recombinantly. Techniques for the manipulation of nucleic acids, such as, e.g., subcloning, labeling probes (e.g., random-primer labeling using Klenow polymerase, nick translation, amplification), sequencing, hybridization and the like are well described in the scientific and patent literature, see, e.g., Sambrook, ed., MOLECULAR CLONING: A LABORATORY MANUAL (2ND ED.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989); CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Ausubel, ed. John Wiley & Sons, Inc., New York (1997); LABORATORY TECHNIQUES IN BIOCHEMISTRY AND MOLECULAR BIOLOGY: HYBRIDIZATION WITH NUCLEIC ACID PROBES, Part I. Theory and Nucleic Acid Preparation, Tijssen, ed. Elsevier, N.Y. (1993). A nucleic acid encoding a polypeptide of the invention is assembled in appropriate phase with a leader sequence capable of directing secretion of the translated polypeptide or fragment thereof.

[0216] The term "isolated" as used herein means that the material, e.g., a nucleic acid, a polypeptide, a vector, a cell, is removed from its original environment, e.g., the natural environment if it is naturally occurring. For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition and still be isolated in that such vector or composition is not part of its natural environment.

[0217] The term "synthetic" as used herein means that the material, e.g. a nucleic acid, has been synthesized in vitro by well-known chemical synthesis techniques, as described in, e.g., Adams (1983) J. Am. Chem. Soc. 105:661; Belousov (1997) Nucleic Acids Res. 25:3440-3444; Frenkel (1995) Free Radic. Biol. Med. 19:373-380; Blommers (1994) Biochemistry 33:7886-7896; Narang (1979) Meth. Enzymol. 68:90; Brown (1979) Meth. Enzymol. 68:109; Beaucage (1981) Tetra. Lett. 22: 1859.

[0218] The term "recombinant" means that the nucleic acid is adjacent to a "backbone" nucleic acid to which it is not adjacent in its natural environment. Backbone molecules according to the invention include nucleic acids such as cloning and expression vectors, self-replicating nucleic acids,

viruses, integrating nucleic acids and other vectors or nucleic acids used to maintain or manipulate a nucleic acid insert of interest. Recombinant polypeptides of the invention, generated from these nucleic acids can be individually isolated or cloned and tested for a desired activity. Any recombinant expression system can be used, including bacterial, mammalian, yeast, insect or plant cell expression systems.

[0219] Also provided is a vector comprising at least one nucleic acid according to the invention. The vector may be a cloning vector, an expression vector or an artificial chromosome.

[0220] As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. Vectors, including cloning and expression vectors, comprise a nucleic acid of the invention or a functional equivalent thereof. Nucleic acids of the invention can be incorporated into a recombinant replicable vector, for example a cloning or expression vector. The vector may be used to replicate the nucleic acid in a compatible host cell. Thus, the invention also provides a method of making polynucleotides of the invention by introducing a polynucleotide of the invention into a replicable vector, introducing the vector into a compatible host cell, and growing the host cell under conditions which bring about replication of the vector. The vector may be recovered from the host cell. Suitable host cells are described below. The vector into which the expression cassette or nucleic acid of the invention is inserted may be any vector which may conveniently be subjected to recombinant DNA procedures, and the choice of the vector will often depend on the host cell into which it is to be introduced. A variety of cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor, N. Y., (1989).

[0221] A vector according to the invention may be an autonomously replicating vector, i.e. a vector which exists as an extra-chromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

[0222] One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication, and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. The terms "plasmid" and "vector" can be used interchangeably herein as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as cosmid, viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses) and phage vectors which serve equivalent functions.

[0223] Vectors according to the invention may be used in vitro, for example for the production of RNA or used to transfect or transform a host cell.

[0224] A vector of the invention may comprise two or more, for example three, four or five, nucleic acids of the invention, for example for overexpression.

[0225] The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vector includes one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operationally linked to the nucleic acid sequence to be expressed.

[0226] Within a vector, such as an expression vector, "operationally linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell), i.e. the term "operationally linked" refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A regulatory sequence such as a promoter, enhancer or other expression regulation signal "operationally linked" to a coding sequence is positioned in such a way that expression of the coding sequence is achieved under condition compatible with the control sequences or the sequences are arranged so that they function in concert for their intended purpose, for example transcription initiates at a promoter and proceeds through the DNA sequence encoding the polypeptide.

[0227] The term "regulatory sequence" or "control sequence" is intended to include promoters, operators, enhancers, attenuators and other expression control elements (e.g., polyadenylation signal). Such regulatory sequences are described, for example, in Goeddel; Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, Calif. (1990).

[0228] The term regulatory or control sequences includes those sequences which direct constitutive expression of a nucleotide sequence in many types of host cells and those which direct expression of the nucleotide sequence only in a certain host cell (e.g. tissue-specific regulatory sequences).

[0229] A vector or expression construct for a given host cell may thus comprise the following elements operationally linked to each other in a consecutive order from the 5'-end to 3'-end relative to the coding strand of the sequence encoding the polypeptide of the invention: (i) a promoter sequence capable of directing transcription of the nucleotide sequence encoding the polypeptide in the given host cell; (ii) optionally, a signal sequence capable of directing secretion of the polypeptide from the given host cell into a culture medium; (iii) optionally, a sequence encoding for a C-terminal, N-terminal or internal epitope tag sequence or a combination of the aforementioned allowing purification, detection or labeling of the polypeptide; (iv) a nucleic acid sequence of the invention encoding a polypeptide of the invention; and preferably also (v) a transcription termination region (terminator) capable of terminating transcription downstream of the nucleotide sequence encoding the polypeptide. Particular named bacterial promoters include lad, lacZ, T3, T7, SP6, K1F, tac, tet, gpt, lambda P_R, P_L and trp. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus and mouse metallothionein-I. Selection of the appropriate vector and promoter

is well within the level of ordinary skill in the art. Downstream of the nucleotide sequence according to the invention there may be a 3' untranslated region containing one or more transcription termination sites (e.g. a terminator). The origin of the terminator is less critical. The terminator can, for example, be native to the DNA sequence encoding the polypeptide. Preferably, the terminator is endogenous to the host cell (in which the nucleotide sequence encoding the polypeptide is to be expressed). In the transcribed region, a ribosome binding site for translation may be present. The coding portion of the mature transcripts expressed by the constructs will include a translation initiating AUG (or TUG or GUG in prokaryotes) at the beginning and a termination codon appropriately positioned at the end of the polypeptide to be translated.

[0230] Enhanced expression of a polynucleotide of the invention may also be achieved by the selection of heterologous regulatory regions, e.g. promoter, secretion leader and/or terminator regions, which may serve to increase expression and, if desired, secretion levels of the protein of interest from the expression host and/or to provide for the inducible control of the expression of a polypeptide of the invention. It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The vectors, such as expression vectors, of the invention can be introduced into host cells to thereby produce proteins or peptides, encoded by nucleic acids as described herein.

[0231] The vectors, such as recombinant expression vectors, of the invention can be designed for expression of a portion or all of a NRPS of the invention in prokaryotic or eukaryotic cells. For example, a portion or all of a NRPS of the invention can be expressed in bacterial cells such as *E. coli, Bacillus* strains, insect cells (using baculovirus expression vectors), filamentous fungi, yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, Calif. (1990). Representative examples of appropriate hosts are described hereafter. Appropriate culture media and conditions for the above-described host cells are known in the art.

[0232] As set out above, the term "control sequences" or "regulatory sequences" is defined herein to include at least any component which may be necessary and/or advantageous for the expression of a polypeptide. Any control sequence may be native or foreign to the nucleic acid sequence of the invention encoding a polypeptide. Such control sequences may include, but are not limited to, a promoter, a leader, optimal translation initiation sequences (as described in Kozak, 1991, J. Biol. Chem. 266:19867-19870), a secretion signal sequence, a pro-peptide sequence, a polyadenylation sequence, a transcription terminator. At a minimum, the control sequences typically include a promoter, and transcriptional and translational stop signals. A stably transformed microorganism is one that has had one or more DNA fragments introduced such that the introduced molecules are maintained, replicated and segregated in a growing culture. Stable transformation may be due to multiple or single chromosomal integration(s) or by (an) extrachromosomal element (s) such as (a) plasmid vector(s). A plasmid vector is capable of directing the expression of polypeptides encoded by particular DNA fragments. Expression may be constitutive or regulated by inducible (or repressible) promoters that enable high levels of transcription of functionally associated DNA fragments encoding specific polypeptides.

[0233] Expression vectors of the invention may also include a selectable marker gene to allow for the selection of bacterial strains that have been transformed, e.g., genes which render the bacteria resistant to drugs such as chloramphenicol, erythromycin, kanamycin, neomycin, tetracycline, as well as ampicillin and other penicillin derivatives like carbenicillin. Selectable markers can also include biosynthetic genes, such as those in the histidine, tryptophan and leucine biosynthetic pathways.

[0234] The appropriate polynucleotide sequence may be inserted into the vector by a variety of procedures. In general, the polynucleotide sequence is ligated to the desired position in the vector following digestion of the insert and the vector with appropriate restriction endonucleases. Alternatively, blunt ends in both the insert and the vector may be ligated. A variety of cloning techniques are disclosed in Ausubel et al. Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. 1997 and Sambrook et al, Molecular Cloning: A Laboratory Manual 2nd Ed., Cold Spring Harbor Laboratory Press (1989). The polynucleotide sequence may also be cloned using homologous recombination techniques including in vitro as well as in vivo recombination. Such procedures and others are deemed to be within the scope of those skilled in the art. The vector may be, for example, in the form of a plasmid, a viral particle, or a phage. Other vectors include chromosomal, nonchromosomal and synthetic polynucleotide sequences, derivatives of SV40; bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and bacteriophage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus and pseudorabies.

[0235] The invention also provides an engineered or recombinant host cell, i.e. a transformed cell comprising a nucleic acid sequence of the invention as a heterologous or non-native polynucleotide, e.g. a sequence encoding the cystobactamide biosynthesis cluster or a NRPS of the invention, or a vector of the invention. The host cell may be any of the host cells familiar to those skilled in the art, including prokaryotic cells, eukaryotic cells, such as bacterial cells, fungal cells, yeast cells, mammalian cells, insect cells, or plant cells.

[0236] Preferred mammalian cells include e.g. Chinese hamster ovary (CHO) cells, COS cells, 293 cells, PerC6 cells, hybridomas, Bowes melanoma or any mouse or any human cell line. Exemplary insect cells include any species of *Spodoptera* or *Drosophila*, including *Drosophila* S2 and *Spodoptera* Sf-9. Exemplary fungal cells include any species of *Aspergillus*. Preferred yeast cell include, e.g. a cell from a *Candida, Hansenula, Kluyveromyces, Pichia, Saccharomyces, Schizosaccharomyces*, or *Yarrowia* strain. More preferably from *Kluyveromyces lactis, S. cerevisiae, Hansenula polymorpha, Yarrowia lipolytica*, or *Pichia pastoris*. According to the invention, the host cell may be a prokaryotic cell. Preferably, the prokaryotic host cell is a bacterial cell. The term "bacterial cell" includes both Gram-negative and Gram-positive as well as archaeal microorganisms. Suitable bacteria may be selected from e.g. *Escherichia, Anabaena, Caulobacter, Gluconobacter, Rhodobacter, Pseudomonas, Paracoccus, Bacillus, Brevibacterium, Corynebacterium, Rhizobium* (*Sinorhizobium*), *Flavobacterium, Klebsiella, Enterobacter, Lactobacillus, Lactococcus, Methylobacterium, Staphylococcus* or *Streptomyces*. Preferably, the bacte-

rial cell is selected from the group consisting of *B. subtilis, B. amyloliquefaciens, B. licheniformis, B. puntis, B. megaterium, B. halodurans, B. pumilus, G. oxydans, Caulobacter crescentus* CB 15, *Methylobacterium extorquens, Rhodobacter sphaeroides, Pseudomonas putida, Paracoccus zeaxanthinifaciens, Paracoccus denitrificans, E. coli, C. glutamicum, Staphylococcus carnosus, Streptomyces lividans, Sinorhizobium melioti* and *Rhizobium radiobacter*. The selection of an appropriate host is within the abilities of those skilled in the art.

[0237] The vector can be introduced into the host cells using any of a variety of techniques, including transformation, transfection, transduction, viral infection, gene guns, or Ti-mediated gene transfer. Particular methods include calcium phosphate transfection, DEAE-Dextran mediated transfection, lipofection, or electroporation (Davis, L., Dibner, M., Battey, I., Basic Methods in Molecular Biology, (1986)). The nucleic acids or vectors of the invention may be introduced into the cells for screening, thus, the nucleic acids enter the cells in a manner suitable for subsequent expression of the nucleic acid. The method of introduction is largely dictated by the targeted cell type.

[0238] Exemplary methods include $CaPO_4$ precipitation, liposome fusion, lipofection (e.g., LIPOFECTIN™), electroporation, viral infection, etc. The candidate nucleic acids may stably integrate into the genome of the host cell (for example, with retroviral introduction) or may exist either transiently or stably in the cytoplasm (i.e. through the use of traditional plasmids, utilizing standard regulatory sequences, selection markers, etc.). As many pharmaceutically important screens require human or model mammalian cell targets, retroviral vectors capable of transfecting such targets can be used.

[0239] Where appropriate, the engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the nucleic acids of the invention. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter may be induced by appropriate means (e.g., temperature shift or chemical induction) and the cells may be cultured for an additional period to allow them to produce the desired polypeptide or fragment thereof. Cells can be harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract is retained for further purification. Microbial cells employed for expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents. Such methods are well known to those skilled in the art. The expressed polypeptide or fragment thereof can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the polypeptide. If desired, high performance liquid chromatography (HPLC) can be employed for final purification steps. The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Depending upon the host employed in a recombinant production procedure, the polypeptides produced by host cells containing the vector may be glycosylated or may be non-glycosylated. Polypeptides of the invention may or may not also include an initial methionine amino acid residue. Cell-free translation systems can also be employed to produce a polypeptide of the invention. Cell-free translation systems can use mRNAs transcribed from a DNA construct comprising a promoter operationally linked to a nucleic acid encoding the polypeptide or fragment thereof. In some aspects, the DNA construct may be linearized prior to conducting an in vitro transcription reaction. The transcribed mRNA is then incubated with an appropriate cell-free translation extract, such as a rabbit reticulocyte extract, to produce the desired polypeptide or fragment thereof.

[0240] Host cells containing the polynucleotides of interest, e.g., nucleic acids of the invention, can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying genes. The culture conditions such as temperature, pH and the like, are those previously used with the host cell selected for expression and will be apparent to the ordinarily skilled artisan. The clones which are identified as having the specified enzyme activity may then be sequenced to identify the polynucleotide sequence encoding a portion or all of a NRPS of the invention.

[0241] Recombinant DNA can be introduced into the host cell by any means, including, but not limited to, plasmids, cosmids, phages, yeast artificial chromosomes or other vectors that mediate transfer of genetic elements into a host cell. These vectors can include an origin of replication, along with cis-acting control elements that control replication of the vector and the genetic elements carried by the vector. Selectable markers can be present on the vector to aid in the identification of host cells into which genetic elements have been introduced. Means for introducing genetic elements into a host cell (e.g. cloning) are well known to the skilled artisan. Other cloning methods include, but are not limited to, direct integration of the genetic material into the chromosome. This can occur by a variety of means, including cloning the genetic elements described herein on non-replicating plasmids flanked by homologous DNA sequences of the host chromosome; upon transforming said recombinant plasmid into a host the genetic elements can be introduced into the chromosome by DNA recombination. Such recombinant strains can be recovered if the integrating DNA fragments contain a selectable marker, such as antibiotic resistance. Alternatively, the genetic elements can be directly introduced into the chromosome of a host cell without use of a non-replicating plasmid. This can be done by synthetically producing DNA fragments of the genetic elements in accordance to the present invention that also contain homologous DNA sequences of the host chromosome. Again if these synthetic DNA fragments also contain a selectable marker, the genetic elements can be inserted into the host chromosome.

[0242] The cystobactamide biosynthesis cluster or a NRPS of the invention may be favorably expressed in any of the above host cells. Thus, the present invention provides a wide variety of host cells comprising one or more of the isolated, synthetic or recombinant nucleic acids and/or NRPSs of the present invention. The host cell, when cultured under suitable conditions, is capable of producing a cystobactamide selected from the group consisting of cystobactamide A, B, C, D, E, F, G and H that it otherwise does not produce, or produces at a lower level, in the absence of a nucleic acid of the invention.

[0243] The invention also relates to an isolated, synthetic or recombinant polypeptide having an amino acid sequence according to any of SEQ ID NOs. 40 to 73, or an amino acid sequence encoded by a nucleic acid of the invention.

[0244] The present invention further provides a method for the preparation of a cystobactamide selected from the group consisting of cystobactamide A, B, C, D, E, F, G and H, said method generally comprising: providing a host cell of the present invention, and culturing said host cell in a suitable culture medium under suitable conditions such that at least one cystobactamide selected from the group consisting of cystobactamide A, B, C, D, E, F, G and His produced. The method may further comprise a step of isolating a cystobactamide selected from the group consisting of cystobactamide A, B, C, D, E, F, G and H, i.e. separating and retaining the compound from the culture broth. The isolation step may be carried out using affinity chromatography, anion exchange chromatography, or reversed phase chromatography.

EXAMPLES

Conditions of Production

Strain for Production

[0245] The strain *Cystobacter velatus* MCy8071 belongs to the order Myxococcales (Myxobacteria), suborder Cystobacterineae, family Cystobacteraceae, genus Cystobacter. The comparison of the partial 16S rRNA gene sequences with sequences of a public database (BLAST, Basic Local Alignment Search Tool provided by NCBI, National Center for Biotechnology Information) revealed 100% similarity to *Cystobacter velatus* strain DSM 14718.

[0246] MCy8071 was isolated at the Helmholtz Centre for Infection Research (HZI, formerly GBF) from a Chinese soil sample collected in 1982. The strain was deposited at the German Collection of Microorganisms in Braunschweig (DSM) in March 2013 under the designation DSM 27004.

Cultivation

[0247] The strain MCy8071 grows well on yeast-agar (VY/2: 0.5% *Saccharomyces cerevisiae,* 0.14% $CaCl_2 \times 2\ H_2O$, 0.5 µg vitamine B_{12}/l, 1.5% agar, pH 7.4), CY-agar (casitone 0.3%, yeast extract 0.1%, $CaCl_2 \times 2\ H_2O$ 0.1%, agar 1.5%, pH 7.2) and P-agar (peptone Marcor 0.2%, starch 0.8%, single cell protein probione 0.4%, yeast extract 0.2%, $CaCl_2 \times 2\ H_2O$ 0.1%, $MgSO_4$ 0.1%, Fe-EDTA 8 mg/l, 1.5% agar, pH 7.5). The working culture was nurtured in liquid medium CY/H (50% CY-medium+50 mM Hepes, 50% H-medium: soy flour 0.2%, glucose 0.8%, starch 0.2%, yeast extract 0.2%, $CaCl_2 \times 2\ H_2O$ 0.1%, $MgSO_4$ 0.1%, Fe-EDTA 8 mg/l, Hepes 50 mM pH 7.4). Liquid cultures were shaken at 180 rpm at 30° C. For conservation aliquots a 2 ml of a three days old culture were stored at −80° C. Reactivation, even after several years, is no problem on the above mentioned agar plates or in 20 ml CY/H-medium (in 100 ml Erlenmeyer flasks with plugs and aluminium-cap). After one-two days the 20 ml cultures can be upscaled to 100 ml.

Morphological Description

[0248] After two days in liquid medium CY/H the rod-shaped cells of strain MCy8071 have a length of 9.0-14.5 µm and width of 0.8-1.0 µm. On the above mentioned agar-plates swarming is circular. On VY/2-agar the swarm is thin and transparent. Yeast degradation is visible on VY/2-agar. On CY-agar the culture looks transparent-orange. On P-agar cell mass production is distinctive and swarming behaviour is reduced. The colony colour is orange-brown. Starch in P-agar is degraded.

[0249] MCy8071 is resistant against the following antibiotics: ampicillin, gentamycin, hygromycin, polymycin, bacitracin, spectinomycin, neomycin, and fusidinic acid. Weak growth is possible with cephalosporin and kasugamycin and no growth is possible with thiostrepton, trimethoprin, kanamycin, and oxytetracycline (final concentration of all antibiotics was adjusted to 50 µg ml^{-1}).

Production of Cystobactamides A, B, C, D, E, F, G and H

[0250] The strain produces in complex media. He prefers nitrogen containing nutrients like single cell protein (Probion) and products of protein decomposition like peptone, tryptone, yeast extract, soy flour and meat extract. Here the production is better with several of the mentioned protein-mixtures compared to a single one.

[0251] Cystobactamides are produced within the logarithmical to the stationary phase of growth. After two days in 100 liter fermentation (medium E) the amount of products did not increase anymore.

[0252] Cystobactamides are delivered to the medium and bind to XAD-adsorber resin. XAD is sieved by a metal sieve and eluted in acetone. Different production temperatures were tested (21° C., 30° C., 37° C. and 42° C.) whereby at 42° C. no production was possible. The optimal temperature was at 30° C. with maximal aeration.

[0253] Fermentation of MCy8071 was conducted in a 150 liter fermenter with 100 liter medium E (skimmed milk 0.4%, soy flour 0.4%, yeast extract 0.2%, starch 1.0%, $MgSO_4$ 0.1%, Fe-EDTA 8 mg/l, glycerine 0.5%; pH 7.4) and in a 100 liter fermenter with 70 liter medium M (soy-peptone 1.0%, maltose 1.0%, $CaCl_2 \times 2\ H_2O$ 0.1%, $MgSO_4$ 0.1%, Fe-EDTA 8 mg/l; pH 7.2) for four days at 30° C. The pH was regulated with potassium hydroxide (2.5%) and sulfuric acid between 7.2 and 7.4. The stirrer speed was 100-400 rpm, aerated with 0.05 vvm compressed air. The dissolved oxygen content within the fermentation broth was regulated by the stirrer speed to pO_2 40%. To bind cystobactamides 1% adsorber resin was added to the fermentation broth. The fermenter was inoculated with 5 liter of a three days old pre-culture (E or M-medium, respectively). The production during the fermentation process was checked by HPLC-MS-analyses and serial dilution test of the methanol extract against *Escherichia coli*. The strain produces Cystobactamides A, B, C, D, E, F, G and H.

Knock-Out Experiments

[0254] To confirm that the cystobactamide biosynthesis gene cluster is responsible for the production of the cystobactamides, a knock-out (KO) experiment was carried out, where CysK (NRPS) and CysL (benzoyl-CoA ligase) was knocked out, respectively. Specifically, PCR products of 1000 bp fragments of CysK and CysL genes were produced from MCy8071 genomic DNA using Taq polymerase. The primers were designed to add 3 stop codons on the extremities of the PCR products.

CysL KO For
TGATTGATTGATCGGCGCGATTCGGCCTCTGG

CysL KO Rev
TCAATCAATCATCGGGTCGCGGTCTCAGGCTC

CysK KO For
TGATTGATTGAAAAACAGTCGGAGGAGTTTCTTGTCC

CysK KO Rev
TCAATCAATCAACTCCCAGTGCCCTCAGCCTC

[0255] The PCR products were gel purified using the Nucleospin® Gel and PCR Clean-up kit from Macherey-Nagel and cloned into a pCR2.1-TOPO vector. The construct was integrated via heat shock into chemically competent *E. coli* HS996 and the selection was done on kanamycin-supplemented LB agar plates. Single colonies were screened for correct constructs via alkaline lysis plasmid preparation and restriction digest by EcoRI. The constructs were then sequenced to ensure the sequence homology.

[0256] A correct construct for each KO was transformed into non-methylating chemically competent *E. coli* SCS110. Plasmids were prepared using the GeneJET Plasmid Miniprep kit from Thermo scientific and integrated into MCy8071 via electroporation. Selection of transformed clones was done on kanamycin-supplemented CTT agar plates. KO mutants and wild type cultures were grown in parallel in the presence of an adsorber resin (XAD-16) and samples of crude extracts of the cultures were analysed.

[0257] The results showed that in the KO mutants there was a complete absence of cystobactamide production indicating that CysK and CysL are essential for the production of the cystobactamides. Furthermore, the result indicates the essential nature of the cystobactamide biosynthesis gene cluster for the production of the cystobactamides.

Structural Analysis:

[0258] HRESI(+)MS analysis of cystobactamide A (1) returned a pseudomolecular formula ion $(M+H)^+$ consistent with the molecular formula $C_{46}H_{45}N_7O_{14}$, requiring twenty eight double bond equivalents (DBE). The ^{13}C NMR (DMSO-d_6) data revealed seven ester/amide carbonyls (δ_C 163.7 to 169.6) and a further 30 sp^2 resonances (δ_C 114.2 to 150.8), accounting for 22 DBE. Consideration of the 1D and 2D NMR data (Table 1) revealed a set of five aromatic spin systems, three of which were attributed to para-substituted, 1,3,4-trisubstituted and 1,2,3,4-tetrasubstituted benzene rings. A set of HMBC correlations from the aromatic signals H-6,6' (δ_H 7.96) and the NH (δ_H 8.92) to the amide carbonyl C-4 (δ_C 166.5); NH (δ_H 10.82) to C-7/7' (δ_C 119.8) and to the second amide carbonyl C-10 (δ_C 164.6); H-12/12 (δ_H 8.20) to C-10 established the connectivity of two of the para-substituted aromatic ring systems (FIG. **1**). Further examination of the ^1H and COSY NMR data established the connectivity of the amide NH (δ_H 8.92) across to the methines H-2 (δ_H 4.96) and H-1 (δ_H 4.70). The downfield characteristic of H-1 (δ_C 79.4) suggested substitution by an oxygen, which was confirmed from a HMBC correlation from H-1 to 1-OMe (δ_H 3.53, δ_C 59.6). Also observed were HMBC correlations from H-1 and H-2 to an ester/amide carbonyl (δ_C 169.6) leading to the construction of subunit A (FIG. **1**).

[0259] For the 1,3,4 trisubstituted benzene ring HMBC correlations were observed from H-17 (δ_H 7.58) to an ester/amide carbonyl C-15 (δ_C 167.3), an oxy quaternary carbon C-18 (δ_C 146.8), C-19 (δ_C 133.6) and C-21 (δ_C 122.9). The isolated spin system for the 1,2,3,4 tetrasubstituted benzene ring showed HMBC correlations from i) H-25 (δ_H 7.82, d, 8.7) to an ester/amide carbonyl C-23 (δ_C 163.7), C-27 (δ_C 136.2) and a quaternary oxy carbon C-29 (δ_C 150.8); ii) H-26 (δ_H 7.42) to C-24 (δ_C 117.3) and C-28 (δ_C 139.5) along with the phenolic hydroxyl (δ_H 11.25) showing correlations to C-24 and C-28) The tri and tetra-substituted benzene rings were attached para to each other by HMBC correlations from the amide NH (δ_H 10.98) to C-20 (δ_C 119.8) C-18 (δ_C 146.7) and C-23 (δ_C 163.7) (FIG. **1**). The last of the para-substituted aromatic spin system H-33/33' (δ_H 8.11, d, 8.3) and H-34/34' (δ_H 7.44, d, 8.3) showed attachment to the 1,2,3-trisubstituted benzene ring by HMBC correlations of the amide NH (δ_H 9.88) and H-33/33' to the amide carbonyl C-31 (δ_C 164.3). Additional interpretation of the COSY data revealed two sets of isopropoxy residues (H_3-39 (δ_H 1.38)-H-38 (δ_H 4.76)-H-40 (δ_H 1.38)) and (H_3-42 (δ_H 1.25)-H-41(δ_H 4.30)-H_3-43(δ_H 1.25). The two isopropoxy residues were confirmed to be attached to the oxy quaternary carbons C-18 (δ_C 146.7) and C-28 (δ_C 139.5) based on ROESY correlations from H-38/H-39 to H-17/NH and H-42/43 to NH/29-OH/H-33/33' (FIG. **1**). A link between subunit A and B was not established, however based on structural similarity to cystobactamide B, the point of attachment of subunits A and B were inferred. Having accounted for majority of the resonances, $N_2O_3H_2$ and 1DBE were left to account for. The UV spectrum of the compound showed a γ_{max} of 301 and 320 nm which suggested a conjugated system which was only possible to have been generated by the attachment of a nitro functionality para- to the aromatic system on subunit A. The remaining MF was adjusted to generate a carboxylic acid residue (C-15) on the 1,2,3-substituted aromatic ring in subunit B generating the 4-amino-3-isopropoxybenzoic acid moiety leading to the construction of the planar structure of cystobactamide A.

[0260] HRESI(+)MS analysis of cystobactamide B (2) returned a pseudomolecular formula ion $(M+H)^+$ consistent with the molecular formula $C_{46}H_{44}N_6O_{15}$, requiring twenty eight double bond equivalents (DBE). The NMR data (Table 2) of 2 was highly similar to (1) with now the NH (δ_H 10.19) and the oxymethine H-1 (δ_H 4.32) seeing the carbonyl C-37 (δ_C 168.6) confirming the point of attachment of subunits A and B. In addition to this the only change was that the carbonyl amide was now adjusted to a carboxylic acid which was later proven by generation of cystobactamide B dimethyl ester.

[0261] HRESI(+)MS analysis of cystobactamide C (3) returned a pseudomolecular formula ion $(M+H)^+$ consistent with the molecular formula $C_{27}H_{29}N_3O_7$, requiring 15 (DBE). The ^1H NMR data for cystobactamide C showed aromatic signals which were reminiscent of cystobactamide A and B, however it lacked aromatic resonances for two sets of para-substituted aromatic units. The COSY data revealed the existing two sets of isopropoxy residues along with one set of para-substituted aromatic ring system. Interpretation of the 1D and 2D NMR data (Table 3, FIG. **2**) identified cystobactamide C (3) bearing resemblance to the eastern part of cystobactamide A and B, consisting of 3-isopropoxybenzoic acid, 2-hydroxy-3-isopropoxybenzamide and a para-aminobenzamide unit.

TABLE 1

NMR (700 MHz, DMSO-d_6) data for cystobactamide A (1)

pos	δ_H, mult (J in Hz)	δ_C*	COSY	HMBC	ROESY
1	4.70, d (6.9)	79.4	2	2, 1-OMe, CO_2NH_2	1-OMe, 3
2	4.96, dd (8.2, 6.9)	55.6	1, 3	1, CO_2NH_2, 4	1-OMe, 3, 34
3	8.92, d (8.2)		2	4	1, 2, 6'
4		166.5			
5		128.6			
6, 6'	7.96, d (8.6)	128.9	7, 7'	4, 6, 6', 8	3
7, 7'	7.91, d (8.6)	119.8	6, 6'	5, 7, 7'	9
8		142.2			
9	10.82, s			7, 7', 10	7', 12'
10		164.6			
11		140.4			
12, 12'	8.20, d (8.6)	129.5	13, 13'	12, 12', 10, 14	9
13, 13'	8.39, d (8.6)	123.8	12, 12'	11, 13, 13', 14	
14		149.6			
15		167.3			
16		126.2			
17	7.58, s	114.2		15, 18, 19, 21,	38, 40
18		146.7			
19		133.6			
20	8.50, d (8.2)	119.8	21	16, 18	21
21	7.60, d (8.2)	122.9	20	15, 17	20
22	10.98, s			18, 20, 23	25, 39
23		163.7			
24		117.3			
25	7.82, d (8.7)	125.2	26	23, 24, 29	22
26	7.42[a]	116.3	25	27, 28	30
27		136.2			
28		139.5			
29		150.8			
30	9.88, s			26, 27, 31	33, 41 , 42, 43
31		164.3			
32		134.0			
33, 33'	8.11, d (8.3)	129.5	34, 34'	31, 33, 33', 35	30, 41, 42, 43
34, 34'	7.44[a]	125.6	33, 33'	34, 34', 32	1-OMe, 2
35		137.3			
36	11.53, s				
37		NO			
1-OMe	3.53, s	59.6		1	1, 2
38	4.76, spt (6.0)	72.1	39, 40		17
39	1.38, d (6.0)	22.1	38	38, 40	22
40	1.38, d (6.0)	22.1	38	38, 39	17
41	4.30, spt (6.0)	76.0	42, 43		30, 42, 43
42	1.25, d (6.0)	22.4	41	41, 43	30, 33'
43	1.25, d (6.0)	22.4	41	41. 42	30, 33'
CO_2NH_2		169.6			
29-OH	11.25, s			27, 28	

[a]Overlapping signals,

*Assignments supported by HSQC and HMBC experiments.

TABLE 2

NMR (700 MHz, DMSO-d_6) data for cystobactamide B (2)

pos	δ_H, mult (J in Hz)	δ_C	COSY	HMBC	ROESY
1	4.31, m[a]	82.0	2	2, 37, CO_2H, 1-OMe,	2, 3, 36, 1-OMe
2	5.07, dd (8.1, 5.6)	54.4	1, 3	CO_2H	1, 1-OMe, 3, 36
3	8.50[b]		2	4	1, 2, 6'
4		166.0			
5		129.3			
6, 6'	7.90, m[c]	128.6	7, 7'	6, 6', 8	
7, 7'	7.90, m[c]	119.8	6, 6'	7, 7'	9
8		141.7			
9	10.79, s			7, 7', 10	7', 12'

TABLE 2-continued

NMR (700 MHz, DMSO-d_6) data for cystobactamide B (2)

pos	δ_H, mult (J in Hz)	δ_C	COSY	HMBC	ROESY
10		164.5			
11		140.5			
12, 12'	8.20, d (8.3)	129.6	13, 13'	12, 12', 14, 10	9
13, 13'	8.38, d (8.3)	123.8	12, 12'	11, 14, 13, 13'	
14		149.6			
15		167.2			
16		125.9			
17	7.58, s	114.2		15, 18, 19, 21,	38, 40
18		146.6			
19		133.5			
20	8.50[b], d (8.4)	119.9	21	16, 18	21
21	7.59, d (8.4)	123.0	20	15, 17	
22	10.98, s			20	25, 39
23		163.9			
24		116.8			
25	7.81, d (8.7)	125.2	26	23, 29	22
26	7.52, d (8.7)	115.6	25	27, 28	30
27		138.8			
28		NO			
29		150.7			
30	9.62, s			31	33, 33', 26, 41, 43
31		164.5			
32		129.3			
33, 33'	7.97, d (8.4)	128.6	34, 34'	31, 33, 33'	30, 41, 42, 43
34, 34'	7.90, m[c]	119.8	33, 33'	34, 34', 32	1-OMe
35		141.7			
36	10.20, s			34, 37	1, 2, 1-OMe
37		168.6			
1-OMe	3.49, s	59.3		1	1, 2, 34, 36
38	4.75, spt (6.0)	72.1	39, 40		17
39	1.38, d (6.0)	22.1	38	38, 40	22
40	1.38, d (6.0)	22.1	38	38, 39	17
41	4.30, m[a]	76.1	42, 43		30, 42, 43
42	1.25, d (6.0)	22.4	41	41, 43	OH
43	1.25, d (6.0)	22.4	41	41. 42	OH, 30, 33'
CO_2H		170.7			
OH	11.22, s			28, 29	

TABLE 3

NMR (500 MHz, DMSO-d_6) data for cystobactamide C (3)

pos	δ_H, mult (J in Hz)	δ_C*	COSY	HMBC
1		167.3		
2		126.1		
3	7.57, s	114.1		1, 5
4		146.8		
5		133.6		
6	8.49, d (8.4)	120.0	7	2, 4
7	7.58, d (8.4)	123.0	6	1, 3, 5
8	10.95, s			6
9		164.0		
10		116.0		
11		150.5		
12		137.5		
13		NO		
14	7.65, d (8.7)	114.5	15	10, 12
15	7.78, d (8.7)	125.3	14	9, 11
16	9.12, s			14, 17
17		164.7		
18		120.4		
19/19'	7.69, d (8.8)	129.4	20/20'	19/19', 21, 17
20/20'	6.62, d (8.8)	113.2	19/19'	18, 20/20'
21		152.8		
22	4.75, m	72.0	23/24	
23/24	1.37, d (6.0)	22.1	22	23/24

TABLE 3-continued

NMR (500 MHz, DMSO-d_6) data for cystobactamide C (3)

pos	δ_H, mult (J in Hz)	δ_C*	COSY	HMBC
25	4.33, m	75.8	26/27	
26/27	1.28, d (6.1)	22.5	25	26/27
OH	11.23, s		25	10

NO—Not Observed,

*Assignments supported by HSQC and HMBC experiments

[0262] HRESI(+)MS analysis of cystobactamide D (4) revealed a pseudomolecular ion ($[M+H]^+$) indicative of a molecular formula ($C_{42}H_{37}O_{14}N_7$) requiring twenty eight double bond equivalents. Interpretation of the NMR (DMSO-d_6) data (Table 4) revealed magnetically equivalent aromatic protons H-12'/12 (δ_H 8.17, d, 8.0) and H-13/13' (δ_H 8.36, d, 8.0) accounting for the first para-substituted benzene ring. Further interpretation of the ^{1}H-^{1}H COSY data revealed the presence of two additional para-substituted benzene rings, (H-35/35') (δ_H 7.80, d, 8.1) and H-36/36' (δ_H 7.94, d, 8.1); the second set of aromatics were heavily overlapped (H-6/6') and (H-7/7' (δ_H 7.88). Diagnostic HMBC correlations of the aromatic protons (H-12/12') to an amide carbonyl C-10 (δ_C 165. 1) along with the exchangable (NH) (δ_H 10.82) coupled to

C-10, C-7/7' established the connectivity of the two para-substituted aromatic rings (FIG. **3**), which was further corraborated by ROESY correlations between NH/H-12 and NH/H-7. The COSY data revealed an additional spin system from an oxymethine H-1 (δ_H 4.08, d, 8.0) through an a-proton H-2 (δ_H 4.91, dd, 8.0, 7.7) to an exchangable proton (NH) O_H 8.47). HMBC correlations from (i) H-2 to three amide carbonyls C-4 (δ_C 166.4), C-15 (δ_C 171.8) and C-32 (δ_C 169.2), (ii) NH (δ_H 8.48) to C-4, (iii) NH (δ_H 10.54) to C-35/35' (δ_C 119.5), (iv) H-6/6' to C-4 further extended the partial structure of cystobactamide D (4). Consideration of the 1-D and 2-D NMR data revealed an additional 1,3,4-trisubstituted and a 1,2,3,4-tetrasubstituted benzene ring. HMBC correlations were observed from the aromatic protons H-27 (δ_H 7.55) and H-29 (δ_H 7.60) to the carbonyl C-31 (δ_C 167.8) and the quaternary carbon C-25 (δ_C 133.0), while H-30 (δ_H 8.47, d, 7.0) and a methoxy signal (δ_H 3.96) were coupled to an oxygen bearing carbon C-26 (δ_C 149.1), hence revealing a 4-amino-3-methoxybenzoic acid moiety, which was later confirmed by esterification. Moreover, HMBC correlations were observed from the exchangeable proton (NH) (δ_H 7.46) to the oxygen bearing carbons C-1 (δ_C 80.8), C-18 (δ_C 141.0) and the aromatic carbon C-22 (δ_C 116.2), while H-22 (δ_H 7.48, d, 8.8) and the methoxy showed couplings to C-18 and H-21 (δ_H 7.77, d, 8.8) coupled to an amide carbonyl C-23 (δ_C 164.8). The presence of a hydroxyl functionality ortho to the methoxy was later confirmed by esterification (4a) (FIG. **4**), revealing the presence of a 4-amino-2-hydroxy-3-methoxybenzamide. The attachment of the 4-amino-3-methoxybenzoic acid and 4-amin0-2-hydroxy-3-methoxybenzamide substituents were confirmed by ROESY and HMBC correlations from the exchangeable NH's observed from the cystobactamide D dimethyl ester (4a). The missing substituents were to be assigned at C-14 (δ_C 150.0) and the carbonyl C-38. The λ_{max} (320 nm) and the downfield chemical shift of C-14 was suggestive of a nitro substituent at C-14 and the primary amine attached to the carbonyl C-38, generating the planar structure of 4.

TABLE 4

NMR (700 MHz, DMSO-d_6) data for cystobactamide D (4)

pos	δ_H, mult (J in Hz)	δ_C	COSY	ROESY	HMBC
1	4.08, d (8.0)	80.7	2		32
2	4.91, dd (8.0, 7.7)	56.4	1, 3	33	1, 4, 15, 32
3	8.47[a]		2		4
4		166.4			
5		129.5			
6/6'	7.91, m[b]	129.0	7/7'		4, 8, 6/6'
7/7'	7.91, m[b]	120.4	6/6'		5, 7/7'
8		142.4			
9	10.82, s			12/12', 7/7'	7, 10
10		165.1			
11		140.9			
12/12'	8.17, d (8.0)	129.9	13/13'	9	10, 12/12', 14
13/13'	8.36, d (8.0)	124.3	12/12'	9	11, 13/13', 14
14		150.0			
15		171.8			
16	NO				
17		129.5			
18		141.0			
19		NO			
20		116.5			
21	7.77, d (8.8)	125.8	22		23
22	7.48, d (8.8)	115.3	21		18, 20
23		164.8			
24	NO				
25		133.0			
26		149.1			
27	7.55, s	111.7			25, 26, 31
28		126.3			
29	7.60[c], d (7.0)	123.3	30		25, 27, 31
30	8.47[a], d, (7.0)	120.1	29		26, 28
31		167.8			
32		169.2			
33	10.54, s			2, 35/35'	
34		142.7			
35/35'	7.80, d, (8.1)	119.5	36/36'	33	35/35', 37
36/36'	7.94, d, (8.1)	129.3	35/35'		34, 36/36', 38
37		129.4			
38		165.5			
1-OMe	3.30, s	58.4			1
18-OMe	3.76, s	61.0			18
26-OMe	3.95, s	56.8			26

[a,b,c]overlapping signals,

^{13}C shifts obtained from 2D HSQC and HMBC experiments.

NO—not observed

TABLE 5

NMR (700 MHz, DMSO-d_6) data for cystobactamide D dimethyl ester (4a)

pos	δ_H, mult (J in Hz)	δ_C	COSY	ROESY	HMBC
1	4.10[a]	80.4	2	3	2
2	4.92, dd (8.0, 7.8)	56.1	1, 3	3, 33	1, 32
3	8.50, d(7.8)		2	1, 2, 6/6'	
4		165.6			
5		129.4			
6/6'	7.91, m[b]	128.8	7/7'	3	4, 8
7/7'	7.91, m[b]	120.1	6/6'		
8		142.0			
9	10.82, s			12/12', 7/7'	7/7'
10		164.8			
11		140.8			
12/12'	8.21, d (8.7)	129.7	13/13'	9, 13/13'	10, 12/12', 14
13/13'	8.39, d (8.7)	124.0	12/12'	12/12'	11, 13/13', 14
14		149.9			
15		NO			
16	9.65, s			18-OMe, 36/36'	38
17		129.5			
18		144.7			
19		152.1			
20		121.8			
21	7.88, d (8.8)	126.1	22		19, 23
22	7.95, d (8.8)	118.9	21		18, 20
23		162.6			
24	10.94, s			19-OMe	30
25		132.8			
26		148.3			
27	7.60, s	111.2		26-OMe	25, 29, 31
28		124.9			
29	7.67, d (8.6)	123.2	30	30	27
30	8.61, d (8.6)	119.1	29	29	
31		166.4			
32		169.2			

TABLE 5-continued

NMR (700 MHz, DMSO-d_6) data for cystobactamide D dimethyl ester (4a)

pos	δ_H, mult (J in Hz)	δ_C	COSY	ROESY	HMBC
33	10.59, s			2, 35/35'	
34		142.8			
35/35'	7.83, d, (8.1)	119.2	36/36'	33	35/35', 37
36/36'	7.97, d, (8.1)	129.1	35/35'	16	34, 36/36', 37, 38
37		129.3			
38		165.5			
1-OMe	3.31	58.1			
18-OMe	3.91, s	61.2		16	18
19-OMe	4.10[a], s	62.0		24	19
26-OMe	4.05	56.7		27	
CO_2Me	3.86, s	52.4			31

[a,b]overlapping signals,
[13]C shifts obtained from 2D HSQC and HMBC experiments.
NO—not observed

[0263] HRESI(+)MS analysis of cystobactamide E (5) revealed a pseudomolecular ion ($[M+H]^+$) indicative of a molecular formula ($C_{26}H_{23}O_9N_5$) requiring eighteen double bond equivalents. The ^1H NMR spectrum was similar to cystobactamide D with the principle difference being the absence of signals reminiscent for the 4-amino-3-methoxybenzoic acid and 4-amino-2-hydroxy-3-methoxybenzamide moieties. Detailed analysis of the 1-D and 2-D NMR data (Table 6) lead to the planar structure of cystobactamide E (5).

TABLE 6

NMR (700 MHz, DMSO-d[6]) data for cystobactamide E (5)

pos	δ_H, mult (J in Hz)	δ_C	COSY	ROESY	HMBC
1	4.08, d (8.2)	80.2	2		1-OMe, 2
2	4.90, dd (8.2, 7.7)	56.1	1, 3	17	1, 4, 15, 16
3	8.50, d (7.7)		2	6/6'	4
4		165.5			
5		129.2			
6/6'	7.91, m[a]	128.6	7/7'	3	4, 6/6', 8
7/7'	7.91, m[a]	120.0	6/6'	9	5, 7/7'
8		142.0			
9	10.82, s			7/7', 12/12'	7/7', 10
10		164.6			
11		140.5			
12/12'	8.21, d (8.4)	129.6	13/13'	9	10, 12/12', 14
13/13'	8.38, d (8.4)	123.9	12/12'		11, 13/13', 14
14		149.9			
15		171.2			
16		168.9			

TABLE 6-continued

NMR (700 MHz, DMSO-d[6]) data for cystobactamide E (5)

pos	δ_H, mult (J in Hz)	δ_C	COSY	ROESY	HMBC
17	10.54, s			2, 19/19', 20/20'	16, 19/19'
18		142.8			
19/19'	7.77, d (8.2)	119.0	20/20'	17	19/19', 21
20/20'	7.90, m[a]	130.6	19/19'	17	18, 20/20', 22
21		125.6			
22		167.2			
1-OMe	3.29	58.1			1

[a]overlapping signals,
[13]C shifts obtained from 2D HSQC and HMBC experiments

[0264] HRESI(+)MS analysis of cystobactamide F (6) returned a pseudomolecular ion $(M+H)^+$ consistent with the molecular Formula $C_{43}H_{39}N_7O_{13}$, requiring 28 DBE. Interpretation of the NMR (DMSO-d_6) data (Table 7) revealed three sets of magnetically equivalent aromatic protons which could be connected via COSY (6/6' and 7/7', 12/12' and 13/13', 33/33' and 34/34') and additionally in contrast to all other cystobactamides a set of magnetically equivalent aromatic protons (26/26' and 27/27') which could be also connected via COSY. These four sets accounted for four para-substituted benzene rings in the molecule instead of three as found in all other cystobactamides. Only one 1,2,3,4-tetra-subsituted benzene ring could be detected where HMBC correlations of the aromatic proton H-22 (d_H 7.22) could be observed to the carbon C-18 (d_C 137.1) and C-20 (d_H 114.0) and from the aromatic proton H-21 (d_H 7.51) to C-23 (d_C 167.3). Protons H-21 and H-22 could be connected via COSY correlations. Since carbons C-17, C-19 and C-22 were not observable, the HR-MS/MS mass of all peptide-fragments has been established and revealed the presence of 7 carbons, 11 protons, one nitrogen and three oxygen in the respective fragment, confirming the presence of a 1,2,3,4 substituted para-amino benzene moiety on this position (see FIG. **1**). HMBC data further confirmed the connection of H-37 (d_H 4.93) to C-18 (d_C 137.1). HMBC and COSY data confirmed an identical linker between the two aromatic parts of the molecule as found in cystobactamide D. HMBC correlations from the exchangeable protons H-9 (d_H 10.82) to C-10 (d_C 163.9) and C-7/7' (d_C 119.4), H-3 (d_H 8.49) to C-4 (d_C 165.1), H-31 (d_H 10.56) to C-30 (d_C 168.3) and C-32 (d_C 141.5) and H-16 (d_H 8.91) to C-36 (d_C 163.1) and C-18 (d_C 137.1) and COSY correlations from H-2 (d_H 4.92) to the exchangeable proton H-3 (d_H 8.49) as well as HRMS fragment data established the serial connectivity of all fragments. The location of the nitro-group and the presence of the free amide group in the linker between the aromatic chains was established using HR-MS/MS fragments to generate the sum-formula of the respective fragments.

TABLE 7

NMR (700 MHz, DMSO-d_6) data for cystobactamide F (6)

pos	δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
1	4.10, d(8.08)	79.7	2	1-OMe, 3	1-OMe, 2, 15, 30
2	4.92, dd(4.10, 4.10)	55.9	1, 3	31	1, 4, 15, 30
3	8.49, d(8.14)		2	1	1, 2, 4
4		165.1			
5		128.7			

TABLE 7-continued

NMR (700 MHz, DMSO-d_6) data for cystobactamide F (6)

pos	δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
6/6'	7.91, m[a]	128.1	7/7'		4, 6/6', 8
7/7'	7.91, m[a]	119.4	6/6'	9	5, 7/7'
8		141.6			
9	10.82, s			7/7', 12/12'	7/7', 8, 10
10		163.9			
11		140			
12/12'	8.21, d(8.71)	129.1	13/13'	9	10, 12/12', 14
13/13'	8.39, d(8.71)	123.3	12/12'		11, 13/13'
14		149			
15		170.6			
16	8.91, s			34/34', 38/38'	18, 36
17		NO			
18		137.1			
19		NO			
20		114.9			
21	7.51, d(9.02)	127.5	22		23
22	7.22, d(9.02)	NO	21		18, 20
23		167.3			
24	15 very broad s				
25		144.5			
26/26'	7.78. d(8.57)	118.4	27/27'		26/26', 28
27/27'	7.86, m[a]	130.1	26/26'		25, 27/27', 29
28		123.4			
29		167.3			
30		168.3			
31	10.56, s			2, 33/33'	30, 33/33'
32		141.5			
33/33'	7.83, m[a]	118.9	34/34'		33/33', 35
34/34'	7.87, m[a]	127.5	33/33'	16	32, 34/34', 36
35		129.2			
36		163.1			
37	4.93, m[a]	71	38/38'		18
38/38'	1.21, d(6.18)	22.4	37	16	37
1-OMe	3.31, s	57.4		1	1

[a]Overlapping signals,
NO = Not Observed,
*Assignments supported by HSQC and HMBC experiments.

[0265] HRESI(+)MS analysis of cystobactamide G (7) returned a pseudomolecular ion $(M+H)^+$ consistent with the molecular Formula $C_{44}H_{41}N_7O_{14}$, requiring 28 DBE. Due to overlapping aromatic signals in DMSO-d_6 the NMR data acquired in Methanol-d_4 was used to establish the partial structures of the aromatic and the linker fragment (Table 8). The para-substituted benzene rings could be established via COSY, HSQC and HMBC correlations. The configuration of the 1,3,4-trisubstituted benzene ring (4-amino-3methoxy-benzamide) and the methoxy-substituent (1-OMe, (d_C 55.2, d_H 3.50) was established via HSQC, COSY and HMBC correlations. Since not all signals on the 1,2,3,4-substituted benzene moiety could be detected in methanol-d_4 the NMR data measured in DMSO-d_6 was interpreted to establish a 4-amino-3-isopropoxy-2-hydroxy-benzamide and an identical linker between the aromatic parts as identified in cystobactamide D. The connection between C-39 (d_C 74.4) and the carbons C-40/40' (d_C 22.7) was established by COSY correlations of H-39 (d_H 4.82) and H-40/40' (d_H 1.31) and the connectivity between the 1,2,3,4-substituted benzene ring and H-39 (d_H 4.82) was established via HMBC correlations of h-39 to C-18 (d_C 137.3 in DMSO-d_6). The configuration of this benzene moiety was further confirmed with HMBC correlations in DMSO-d_6 of H-22 (d_H 7.04) to C-18 (d_C 137.3) and C-20 (d_C 116.1) and HMBC correlations of H-21 (d_H 7.45) to C-23 (d_C 165.4) as well as COSY correlations from H-21 to H-22. The overall sequence, the location of the nitro-group and the presence of the free amide group in the linker between the aromatic chains was established using HR-MS/MS fragments to generate the sum-formula of the respective fragments.

TABLE 8

NMR (700 MHz, Methanol-d_4) data for cystobactamide G (7), including (700 MHz, DMSO-d_6) data for dos. 17-23 and 39-40/40'.

pos	δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
1	4.17, d(7.45)	82.1	2		1-OMe, 2, 15, 32
2	5.08, d(7.37)	57.2	1		1, 4, 15, 32
3	NO				
4		168.9			
5		130.5			
6/6'	7.93, m[a]	129.4	7/7'		4, 6/6', 8
7/7'	7.89, d(8.83)	121.1	6/6'		5, 7/7'
8		142.9			
9	NO				
10		166.5			
11		141.6			
12/12'	8.16, d(8.77)	129.9	13/13'		10, 12/12', 14
13/13'	8.38, d(8.74)	124.5	12/12'		11, 13/13'
14		150.9			
15		174.4			
16	NO				

TABLE 8-continued

NMR (700 MHz, Methanol-d_4) data for cystobactamide G (7), including (700 MHz, DMSO-d_6) data for dos. 17-23 and 39-40/40'.

pos	δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
17		139.4			
18	NO	NO			
19		NO			
20		NO			
21	7.74, d(8.83)	125.4	22		23, 17
22	7.51, broad d	NO			
23		168.7			
24	NO				
25		133.5			
26		149.9			
27	7.67, s	112.7			25, 26, 28. 29, 31
28		131.8			
29	7.61, d(8.22)	129.9	30		27, 30, 31
30	8.45, broad d	120.5	29		
31		174.8			
32		169.5			
33	NO				
34		142.8			
35/35'	7.83, d(8.64)	120.8	36/36'		35/35', 37
36/36'	7.93, m[a]	128.9	35/35'		34, 36/36', 38
37		131.2			
38		166.4			
39	4.82, water peak	74.4	40/40'		40
40/40'	1.31, d(6.13)	22.7	39		39
1-Ome	3.50, s	55.2			1
26-Ome	4.02, s	55.9			26
17		NO			
18		137.3			
19		NO			
20		116.1			
21	7.45, d(8.83)	123.9	22		23
22	7.04, d(8.66)	99.7	21		18, 20
23		165.4			

TABLE 8-continued

NMR (700 MHz, Methanol-d_4) data for cystobactamide G (7), including (700 MHz, DMSO-d_6) data for dos. 17-23 and 39-40/40'.

pos	δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
39	5.05, m	69.7	40/40'		18, 40/40'
40/40'	1.17, d(5.98)	22.5	39		39

[a]Overlapping signals,
NO = Not Observed,
*Assignments supported by HSQC and HMBC experiments.

[0266] HRESI(+)MS analysis of cystobactamide H (8) returned a pseudomolecular ion $(M+H)^+$ consistent with the molecular Formula $C_{43}H_{39}N_7O_{14}$, requiring 28 DBE. The linker configuration between the aromatic chains was found to be identical as the one found in cystobactamide D. interpretation of HSQC, HMBC and COSY data acquired in DMSO-d_6 revealed three para-substituted benzene units as found in cystobactamide A, B, D, F and G. Further interpretation of the COSY, HSGC and HMBC data revealed a identical 1,3,4-trisubstituted benzene moiety which showed HMBC correlations to a methoxy group as found in all other cystobactamides except cystobactamide F (confirmed by HMBC correlation of 1-OMe (d_H 3.27) to C-26 (d_C 147.4)). Analysis of the NMR data revealed—in accordance with the other cystobactamides—a 1,2,3,4-substituted benzene moiety. Significant change came from the establishment of a ethoxy unit via COSY correlation of methylene protons H-39 (d_H 4.17) to methyl group H-40 (d_H 1.27) and the HMBC correlations of methylene group H-39 (d_H 4.17) to C-18 (d_C 139.5) expanding thereby the substitution pattern of the 4-amino-2-hydroxy-3-X-benzamide moiety to X=methoxy, isoproropoxy or ethoxy on position 3. The sequential sequence of cystobactamide H was established by HMBC correlations of the exchangeable protons H-9 (d_H 10.93) to C-10 (d_C 163.9) and C-7/7' (d_C 119.6), H-33 (d_H 10.85) to C-32 (d_C 168.7) and C-35/35' (d_C 118.8), H-16 (d_H 8.91) to C-38 (d_C 163.1), C-18 (d_C 139.5) and C-22 (d_C 100.4) and H-24 (d_H 14.71) to C-20 (d_C 116.1), C-25 (d_C 131.0), C-26 (d_C 147.4) and C-30 (d_C 118.5) and H-2 (d_H 4.85) to C-4 (d_C 165.5) as well as HR-MS2 fragmentation-data which also enabled the localisation of the nitro-group and the establishment of the free amide group in the linker moiety.

TABLE 9

NMR (700 MHz, DMSO-d_6) data for cystobactamide H (8)

pos	Δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
1	4.22, d (8.60)	79.8	2	3, 33	2, 32, 1-OMe
2	4.85, dd (8.42, 8.42)	56.3	1,3	3, 33	1, 4, 15, 32
3	9.02 s		2		
4		165.5			
5		128.8			
6/6'	7.93 m[a]	128.3	7/7'		4, 6/6', 8
7/7'	7.91 m[a]	119.6	6/6'		5, 7/7'
8		141.7			
9	10.93 s			7/7', 12/12'	
10		163.9			
11		140.3			
12/12'	8.22, d(8.72)	129.4	13/13'		10, 12/12', 14
13/13'	8.38, d(8.72)	123.5	12/12'		11, 13/13'
14		149.2			
15		170.7			
16	8.91 s			22, 39, 40	18, 22, 38
17		NO			

TABLE 9-continued

NMR (700 MHz, DMSO-d_6) data for cystobactamide H (8)

pos	Δ_H, mult (J in Hz)	δ_C*	COSY	ROESY	HMBC
18		139.5			
19		NO			
20		116.1			
21	7.45, d(8.63)	124.1	22		18, 23
22	6.95, d(8.66)	100.4	21	16	18
23		165.8			
24	14.71 s			26-OMe, 39	23, 25, 26, 30
25		131.0			
26		147.4			
27	7.46, s	111.1			25, 26, 29, 28, 31
28		133.9			
29	7.38, m[a]	121.3	30		27, 28, 30
30	8.44, d(8.29)	118.5	29		25, 26, 28,
31		169.9			
32		168.7			
33	10.85 s			1, 2, 35/35'	35/35'
34		141.9			
35/35'	7.85, m[a]	118.8	36/36'		37
36/36'	7.85, m[a]	127.7	35/35'		34, 38
37		129.5			
38		163.1			
39	4.17, q(7.03)	65.4	40		18, 40
40	1.27, t(7.07)	15.7	39		39
1-Ome	3.27, s	57.4			1
26-Ome	3.84, s	55.2			26

[a]Overlapping signals,
NO = Not Observed,
*Assignments supported by HSQC and HMBC experiments.

FIGURES

[0267] FIG. **1**: Key 2D NMR correlations (700 MHz, DMSO-d_6) for cystobactamide A (1)

[0268] FIG. **2**: Key 2D NMR correlations (500 MHz, DMSO-d_6) for cystobactamide C (3)

[0269] FIG. **3**: Key 2D NMR correlations (700 MHz, DMSO-d_6) for cystobactamide D (4)

[0270] FIG. **4**: Key 2D NMR correlations of cystobactamide D dimethyl ester (4a)

[0271] FIG. **5**: Key 2D NMR correlations of cystobactamide E (5)

[0272] FIG. **6**: Key 2D NMR correlations (700 MHz, DMSO-d_6) of cystobactamide F (6)

[0273] FIG. **7**: Key 2D NMR correlations (700 MHz, MeOH-d_4) of cystobactamide G (7)

[0274] FIG. **8**: Key 2D NMR correlations (700 MHz, DMSO-d_6) of cystobactamide H (8)

BIOLOGICAL EVALUATION OF CYSTOBACTAMIDES

[0275] As summarized in Tables 10a/b, cystobactamides were evaluated against several microorganisms and cell lines. All derivatives demonstrated a potent inhibitory effect on various *E. coli* strains, including a nalidixic acid resistant (NAL^R) isolate. Overall potency (average MIC values) of the tested derivatives increased in the following order: CysA1, CysC<CysB<CysA, CysG<CysF. Importantly, the pathogenic Gram-negative strains *A. baumannii* and *P. aeruginosa* were also inhibited by the most active derivatives, CysA, CysB, CysG, and CysF, in the low μg/ml range, which is in terms of MIC values only by one order of magnitude higher than for the reference drug ciprofloxacin.

[0276] Average MIC values on Gram-positive bacteria, such as *E. faecalis, S. aureus*, and *S. pneumonia* were partly in the sub-μg/ml range and the average potency of CysA and CysB exceeded that of ciprofloxacin.

[0277] Furthermore, it was shown that cystobactamides do not inhibit the growth of yeast and mammalian cells, respectively. Thus, the cystobactamides did not cause apparent cytotoxicity.

Susceptibility of Mutant *E. coli* Strains to Cystobactamides

[0278] Quinolones are a widely used class of antibiotics that target the type II topoisomerases, DNA gyrase and topoisomerase IV. Resistance to quinolones is thereby often mediated by mutations in chromosomal genes that lead to alterations in the drug targets. In GyrA the quinolone-resistance determining region (QRDR) is located between amino acids 67 and 106, whereas amino acids 83 (Ser) and 87 (Asp) are most often involved.[1,2] In analogous regions of ParC, the secondary target of quinolones, changes of amino acid 80 (Ser) are found to confer quinolone resistance.[3,4]

[0279] Cystobactamides were screened using a panel of *E. coli* strains with typical mutations in gyrA and parC genes (Table 11). With ciprofloxacin the MIC values increase approximately by factor 30 for the single-step gyrA mutations (strain MI and WT-3.2). However, a combination of both gyrA mutations (strain WT-3) results already in nearly clinical resistance (1 mg/L). A parC mutation (strain WT-4 M2.1) leads to a two-fold increase of the MIC of ciprofloxacin. However, MIC values for cystobactamides did not or only marginally increase for gyrA and parC mutant *E. coli* strains, which suggests that cystobactamides might interfere with amino acids 87 and 83 of GyrA and amino acid 80 of ParC to a lower extent than observed for ciprofloxacin.

[0280] High-level quinolone resistance often results from a combination of several target site mutations and altered efflux

mechanisms. The in vitro selected mutant WT III (marR Δ74 bp) does not produce functional MarR, which acts as a repressor of marA expression. This, in turn, leads to overproduction of MarA and AcrAB and overexpression of the AcrAB efflux pump is associated with the MAR (multiple antibiotic resistance) phenotype.[5] *E. coli* strain WT III was less susceptible to ciprofloxacin treatment by a factor of ca. 4 (cp. *E. coli* WT). In comparison, MIC values of cystobactamides B, F, and G were still in the μg/ml range. Notably, the MIC of CysF on strain *E. coli* WT III only increased by factor 2 compared to wildtype *E. coli* DSM-1116, whereas the MIC of ciprofloxacin increased by ca. factor 10.

TABLE 10a

Antimicrobial activity of cystobactamides (Cys).

Test organism	CysA	CysA1	CysB	CysC
	MIC [μg/ml]			
Acinetobacter baumannii DSM-30008	7.4	58.9	3.7	32.5
Burkholderia cenocepacia DSM-16553	>59	>59	>59	>65
Chromobacterium violaceum DSM-30191	>59	>59	14.7	16.3
Escherichia coli DSM-1116	0.9	14.7	1.8	16.3
Escherichia coli DSM-12242 (NAL^R)	0.9	29.4	3.7	8.1
Escherichia coli DSM-26863 (tolC3)	0.5	7.4	1.8	4.1
Escherichia coli ATCC35218	0.9	14.7	1.8	16.3
Escherichia coli ATCC25922	0.5	7.4	0.9	8.1
Enterobacter aerogenes DSM-30053	>59	>59	>59	>33
Klebsiella pneumoniae DSM-30104	>59	>59	>59	65
Pseudomonas aeruginosa PA14	>59	58.9	14.7	65
Pseudomonas aeruginosa ATCC27853	>59	58.9	14.7	65
Mycobacterium smegmatis mc^2155 ATCC700084	>59	>59	>59	>65
Bacillus subtilis DSM-10	0.12	1.8	0.46	2.0
Enterococcus faecalis ATCC29212	0.06	3.7	0.23	4.1
Micrococcus luteus DSM-1790	0.06	7.4	0.23	4.1
Staphylococcus aureus ATCC29213	0.12	14.7	0.12	8.1
Streptococcus pneumoniae DSM-20566	0.23	14.7	0.46	8.1
Candida albicans DSM-1665	>59	>59	>59	>65
Pichia anomala DSM-6766	>59	>59	>59	>65

Test organism	CysF	CysG	CIP
	MIC [μg/ml]		
Acinetobacter baumannii DSM-30008	—	—	0.2
Burkholderia cenocepacia DSM-16553	—	—	6.4
Chromobacterium violaceum DSM-30191	—	—	0.006
Escherichia coli DSM-1116	0.4	0.9	0.006
Escherichia coli DSM-12242 (NAL^R)	—		0.05
Escherichia coli DSM-26863 (tolC3)	0.4	0.9	≤0.003
Escherichia coli ATCC35218	—	—	0.006
Escherichia coli ATCC25922	—	—	≤0.003
Enterobacter aerogenes DSM-30053	—	—	0.2
Klebsiella pneumoniae DSM-30104	—	—	0.025
Pseudomonas aeruginosa PA14	3.4	7.1	0.1
Pseudomonas aeruginosa ATCC27853	—	—	0.1
Mycobacterium smegmatis mc^2155 ATCC700084	—	—	0.4
Bacillus subtilis DSM-10	—	—	0.1
Enterococcus faecalis ATCC29212	—	—	0.8
Micrococcus luteus DSM-1790	—	—	1.6
Staphylococcus aureus ATCC29213	—	—	0.1
Streptococcus pneumoniae DSM-20566	—	—	1.6

TABLE 10a-continued

Antimicrobial activity of cystobactamides (Cys).

Candida albicans DSM-1665	—	—	>6.4
Pichia anomala DSM-6766	—	—	>6.4

CIP reference antibiotic ciprofloxacin
— not determined

TABLE 10b

Cytotoxicity of cystobactamides (Cys).

Cell lines and primary cells	GI_{50} [μM] CysA	CysA1	CysB
CHO-K1 (Chinese hamster ovary)	37-111	>111	>111
HCT-116 (human colon carcinoma)	—	—	>50
HUVEC (human umbilical vein endothelial cells)	—	—	>50

Cell lines and primary cells	GI_{50} [μM] CysC	CysF	CysG
CHO-K1 (Chinese hamster ovary)	ca. 111	>111	37-111
HCT-116 (human colon carcinoma)	—	—	—
HUVEC (human umbilical vein endothelial cells)	—	—	—

— not determined

TABLE 11

Antimicrobial activity of cystobactamides (Cys) against *E. coli* mutant strains.

Test organism [resistance mutations]	CysA	CysA1	CysB	CysC
	MIC [μg/ml]			
Escherichia coli WT	0.5	14.7	1.8	8.1
Escherichia coli MI [gyrA(S83L)]	3.7	29.4	3.7	16.3
Escherichia coli WT-3.2 [gyrA(D87G)]	3.7	29.4	3.7	32.5
Escherichia coli WT-3 [gyrA(S83L, D87G)]	14.7	>59	7.4	>33
Escherichia coli WT-4 M2.1 [parC(S80I)]	0.5	14.7	1.8	8.1
Escherichia coli MI-4 [gryM(S83L), parC(S80I)]	0.5	14.7	1.8	16.3
Escherichia coli WTIII [marRΔ74bp]	14.7	58.9	3.7	65

Test organism [resistance mutations]	CysF	CysG	CIP
	MIC [μg/ml]		
Escherichia coli WT	—	—	0.013
Escherichia coli MI [gyrA(S83L)]	—	—	0.4
Escherichia coli WT-3.2 [gyrA(D87G)]	—	—	0.4
Escherichia coli WT-3 [gyrA(S83L, D87G)]	—	—	0.8
Escherichia coli WT-4 M2.1 [parC(S80I)]	—	—	0.025
Escherichia coli MI-4 [gyrA(S83L), parC(S80I)]	—	—	0.4
Escherichia coli WTIII [marRΔ74bp]	0.9	3.6	0.05

CIP reference antibiotic ciprofloxacin
— not determined

Experimental Procedures Cell-Based Assays

[0281] Cell lines and primary cells. Human HCT-116 colon carcinoma cells (CCL-247) were obtained from the American Type Culture Collection (ATCC) and Chinese hamster ovary CHO-K1 cells (ACC-110) were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ). Both cell lines were cultured under the conditions recom-

mended by the respective depositor. Primary HUVEC (human umbilical vein endothelial cells; single donor) were purchased from PromoCell (Heidelberg, Germany) and cultured in Endothelial Cell Growth Medium (PromoCell) containing the following supplements: 2% FCS, 0.4% ECGS, 0.1 ng/ml EGF, 1 ng/ml bFGF, 90 μg/ml heparin, 1 μg/ml hydrocortisone.

[0282] Bacterial Strains.

[0283] Bacterial wildtype strains used in susceptibility assays were either part of our strain collection or purchased from the German Collection of Microorgansims and Cell Cultures (DSMZ) or from the American Type Culture Collection (ATCC). *E. coli* strain WT[6] and *E. coli* mutants were kindly provided by Prof. Dr. P. Heisig, Pharmaceutical Biology and Microbiology, University of Hamburg.

[0284] Cytotoxicity Assay.

[0285] Cells were seeded at 6×10^3 cells per well of 96-well plates (Corning CellBind®) in complete medium (180 μl) and directly treated with cystobactamides dissolved in methanol in a serial dilution. Compound were tested in duplicate for 5 d, as well as the internal solvent control. After 5 d incubation, 5 mg/ml MTT in PBS (20 μL) was added per well and it was further incubated for 2 h at 37° C.[7] The medium was then discarded and cells were washed with PBS (100 μl) before adding 2-propanol/10N HCl (250:1, v/v; 100 μl) in order to dissolve formazan granules. The absorbance at 570 nm was measured using a microplate reader (EL808, Bio-Tek Instruments Inc.).

[0286] Susceptibility Testing.

[0287] MIC values were determined in microdilution assays. Overnight cultures were diluted in the appropriate growth medium to achieve an inoculum of 10^4-10^6 cfu/mL. Yeasts were grown in Myc medium (1% phytone peptone, 1% glucose, 50 mM HEPES, pH 7.0), *S. pneumonia* and *E. faecalis* in tryptic soy broth (TSB: 1.7% peptone casein, 0.3% peptone soymeal, 0.25% glucose, 0.5% NaCl, 0.25% K_2HPO_4; pH 7.3); *M. smegmatis* in Middlebrook 7H9 medium supplemented with 10% Middlebrook ADC enrichment and 2 ml/l glycerol). All other listed bacteria were grown in Müller-Hinton broth (0.2% beef infusion solids, 1.75% casein hydrolysate, 0.15% starch, pH 7.4). Cystobactamides and reference drugs were added directly to the cultures in sterile 96-well plates as duplicates and serial dilutions were prepared. Microorganisms were grown on a microplate shaker (750 rpm, 30-37° C., 18-48 h), except *S. pneumonia*, which was grown at non-shaking conditions (37° C., 5% CO_2, 18 h). Growth inhibition was assessed by visual inspection and the MIC was defined as the lowest concentration of compound that inhibited visible growth.

Target Identification

[0288] To test the anti-gyrase activity of cystobactamides, commercial *E. coli* gyrase supercoiling kits (Inspiralis) were used. Cystobactamide A inhibited the *E. coli* gyrase (20.5 nM eq. 1 unit) showing an apparent IC_{50} of 6 μM. Cystobactamide A1 inhibited the *E. coli* gyrase (20.5 nM eq. 1 unit) showing an apparent IC_{50} of 2.5 μM. Cystobactamide D inhibited the *E. coli* gyrase (20.5 nM eq. 1 unit) showing an apparent IC_{50} of 1 μM. Cystobactamide C inhibited the *E. coli* gyrase (20.5 nM eq. 1 unit) showing an apparent IC_{50} of 7.7 μM. Cystobactamides thus are novel inhibitors of bacterial DNA gyrase.

[0289] IC_{50} values of cystobactamide A-D in the Gyrase inhibition assay:

Compound	IC_{50}/μM
cystobactamide A	6 +/− 1.4
cystobactamide A1	2.5 +/− 0.8
cystobactamide C	7.2 +/− 0.74
cystobactamide D	0.7 +/− 0.4

[0290] FIG. **9***a* show the results of the Gyrase inhibition assay. The gyrase reactions were titrated with varying concentrations of cystobactamide A, A1, C and D and resolved by agarose gel electrophoresis. For IC_{50} determination the band intensity of the supercoiled plasmid was determined using Adobe Photoshop, plotted vs. [cystobactamide] and fitted using Hill's equation.

[0291] Prokaryotic DNA gyrase and topoisomerase IV share a high degree of homology and gyrase inhibitors typically show a topoisomerase IV inhibitory activity.[8] To test the influence of the cystobactamides on topoisomerase IV a commercial *E. coli* topoisomerase IV kit (Inspiralis) was used.

[0292] Cystobactamide A inhibited the activity of *E. coli* topo IV only at the highest tested concentration of 815 μM. Cystobactamide A1 inhibited *E. coli* topo IV showing an IC_{50} value of 6.4+/−1.8 μM. Cystobactamide C inhibited the activity of *E. coli* topo IV only at the highest tested concentration of 300 μM. Cystobactamide D inhibited *E. coli* topo IV showing an IC_{50} value of 10+/−3 μM.

[0293] IC_{50} values for cystobactamide A-D in the *E. coli* Topoisomerase IV inhibition assay:

Compound	IC_{50}/μM
cystobactamide A	>160
cystobactamide A1	6.4 +/− 1.8
cystobactamide C	>60
cystobactamide D	10 +/− 3

[0294] FIG. **9***b* shows the result of the Topoisomerase IV inhibition assay. The topo IV reactions were titrated with varying concentrations of A-D and resolved by agarose gel electrophoresis. For IC_{50} determination the band intensity of the supercoiled plasmid was determined using Adobe Photoshop, plotted vs. [cystobactamide] and fitted using Hill's equation.

[0295] Prokaryotic DNA topoisomerase IV and eukaryotic topoisomerase II share a high degree of homology (type IIa topoisomerases) and inhibitors of the prokaryotic enzyme often also inhibits the eukaryotic counterpart.[8] To test the influence of the cystobactamides on eukaryotic topoisomerase IV a commercial *H. sapiens* topoisomerase II kit (Inspiralis) was used.

[0296] Cystobactamide A inhibited the activity of human topo II only at the highest tested concentration of 815 μM. Cystobactamide A1 inhibited human topo II showing an IC_{50} value of 9+/−0.03 μM. Cystobactamide C inhibited the activity of human topo II only at the highest tested concentration of 300 μM. Cystobactamide D inhibited human topo II showing an IC_{50} value of 41.2+/−3 μM

[0297] IC_{50} values for cystobactamide A-D in the *H. sapiens* Topoisomerase II inhibition assay:

Compound	IC_{50}/μM
cystobactamide A	>160
cystobactamide A1	9 +/− 0.03
cystobactamide C	>60
cystobactamide D	41.2 +/− 3

[0298] FIG. **9***c* shows the result of the Topoisomerase II inhibition assay. The topo II reactions were titrated with varying concentrations of A-D and resolved by agarose gel electrophoresis. For IC_{50} determination the band intensity of the supercoiled plasmid was determined using Adobe Photoshop, plotted vs. [cystobactamide] and fitted using Hill's equation.

[0299] Aside the ATP-dependent type IIa topoisomerases like *E. coli* gyrase, topoIV and human topoII, the activity of cystobactamides on the ATP-independent human topoisomerase I was tested as well.

[0300] IC_{50} values for cystobactamide A-D in the *H. sapiens* Topoisomerase I inhibition assay:

Compound	IC_{50}/μM
cystobactamide A	~10
cystobactamide A1	~0.7
cystobactamide C	~6
cystobactamide D	~33.6

[0301] FIG. **9***d* shows the result of the Topoisomerase I inhibition assay. The topo I reactions were titrated with varying concentrations of A-D and resolved by agarose gel electrophoresis. For IC_{50} determination the band intensity of the supercoiled plasmid was determined using Adobe Photoshop, plotted vs. [cystobactamide] and fitted using Hill's equation.

[0302] IC_{50}(gyrase) vs. IC_{50}(topoisomerase IV) value comparison of cystobactamide A-D:

	IC_{50}/μM		ratios
ratios	gyrase	Topo IV	IC_{50}(topo IV)/IC_{50}(gyrase)
cystobactamide A	6	~815	~136
cystobactamide A1	2.5	6.4	~2.6
cystobactamide D	0.7	10	~14
cystobactamide C	7.2	~300	~42

[0303] Cystobactamides A and C show a strong preference for gyrase as molecular target (40-100 fold stronger preference for gyrase). A1 and D both target gyrase and topoisomerase IV almost equally well (2.6-10 fold stronger preference for gyrase).

[0304] Generally, there are two described inhibition modes/binding sites for gyrase inhibitors:

[0305] 1. Compounds like the fluoroquinolones bind to the GyrA DNA complex and avoid the religation of the nicked dsDNA (gyrase poisoning); and

[0306] 2. Aminocoumarins on the other hand bind to the ATP binding pocket on GyrB (competitive inhibition).8

[0307] To test if cystobactamides follow any of those two inhibition modes, DNA/gyrase complex linearization assays (A) and ATP competition assays (B) were performed using cystobactamide D. (A) Here, the complex of DNA and gyrase is trapped using SDS and the gyrase is digested using proteinase K. If the gyrase/DNA complex is trapped by a gyrase inhibitor of type 1 this will lead to the formation of linearized plasmid (as the religation is inhibited). Type 2 inhibitor-bound or compound-free samples will not show the formation of linearized plasmids. The results of the assay are shown in FIG. **10***a*. Ciprofloxacin (a known gyrase/DNA stabilizer) and cystobactamide D show the formation of linearized plasmid after proteinase K treatment. This effect is not seen for the untreated control. Therefore, it appears likely that cystobactamides stabilize the covalent GyrA-DNA complex in a fashion comparable to the fluoroquionolones. (B) Here, standard gyrase reactions were inhibited using a constant amount of cystobactamide D and titrated with increasing amounts of ATP. If ATP and cystobactamide D would compete for binding at the ATP binding pocket on the gyrase GyrB subunit, increasing amounts of ATP would lead to the formation of supercoiled plasmid in the assay. FIG. **10***b* shows the assay results. Even at the highest ATP concentration of 10 mM (2000 fold cystobactamide concentration) the gyrase activity is not regained, indicating that the ATP binding pocket is not the binding site of the cystobactamides. This result is in line with the linearization assay results.

[0308] FIG. **11** shows the results of the DNA/gyrase complex linearization assay.

Experimental Procedures

Gyrase Supercoiling Assay

[0309] To test the anti-gyrase activity of cystobactamides, commercial *E. coli* gyrase supercoiling kits (Inspiralis, Norwich, UK) were used.3 For standard reactions 0.5 μg relaxed plasmid were mixed with 1 unit (~20.5 nM) *E. coli* gyrase in 1× reaction buffer (30 μl final volume, see kit manual) and incubated for 30 minutes at 37° C. The reactions were quenched by the addition of DNA gel loading buffer containing 10% (w/v) SDS. The samples were separated on 0.8% (w/v) agarose gels and DNA was visualized using Roti-GelStain (Carl Roth).

[0310] All natural products stock solutions and dilutions were prepared in 100% DMSO and added to the supercoiling reactions giving a final DMSO concentration of 5% (v/v). Ciprofloxacin stock solutions and Dilutions were prepared in 10 mM HCl and 50% DMSO and used 1:10 in the final assay.

[0311] Following natural product concentrations were used in the assay:

[0312] Cystobactamide A: 815.8 μM; 163 μM; 80 μM, 16 μM; 8 μM; 1.6 μM; 0.8 μM; 0.16 μM; 0.08 μM; 0.016 μM

[0313] Cystobactamide A1: 543.5 μM; 108.7 μM; 54 μM; 10.8 μM; 5.4 μM; 1.087 μM; 0.54 μM; 0.108 μM; 0.054 μM; 0.0108 μM

[0314] Cystobactamide C: 300 μM; 60 μM; 30 μM; 6 μM; 3 μM; 0.6 μM; 0.3 μM; 0.06 μM; 0.03 μM; 0.006 μM

[0315] Cystobactamide D: 347 μM; 173.5 μM; 86.75 μM; 43.38 μM; 21.69 μM; 10.84 μM; 5.42 μM; 2.71 μM; 1.36 μM; 0.68 μM; 0.34 μM; 0.17 μM; 0.085 μM; 0.042 μM; 0.021 μM; 0.0106 μM; 0.0053 μM

[0316] Control reactions were: no enzyme and a standard reaction in presence of 5% (v/v) DMSO.

[0317] All reaction samples were equilibrated for 10 minutes at room-temperature in the absence of DNA. Then the relaxed plasmid was added to start the reaction.

Proteinase K Linearization Assay

[0318] To test if cystobactamides stabilize the covalent complex between DNA gyrase and the nicked DNA substrate,

proteinase K linearization assay were performed (see a). Standard gyrase supercoiling assays were run in the presence of cystobactamide D (18 μM; 1.8 μM). Control reactions contained no gyrase, no inhibitor or the known gyrase/DNA complex stabilizer ciprofloxacin (1 μM). The reactions were quenched by the addition of 1/10 volume of 10% SDS. To linearize the nicked DNA-gyrase complexes, 50 μg/ml proteinase K were added to the reactions and incubated for 30 minutes at 37° C. The samples were separated on 0.8% (w/v) agarose gels and DNA was visualized using Roti-GelStain (Carl Roth). To detect linearized plasmid bands the relaxed plasmid was digested by the single-cutting restriction enzyme NdeI.

Gyrase Supercoiling Assay with Varying ATP Concentrations

[0319] To test if cystobactamides compete with ATP for binding to the ATP binding pocket on GyrB, standard gyrase supercoiling assays (see a) with varying ATP concentrations were performed. Standard reaction mixes (1 mM ATP) were supplemented with ATP (0.5M ATP stock solution, ATP was purchased from Sigma-Aldrich) to final ATP concentrations of 2.5; 5 and 10 mM. All reactions were performed in triplicates.

Topoisomerase IV Relaxation Assay

[0320] To test the anti-topoisomerase IV activity of cystobactamides, commercial *E. coli* topoisomerase IV relaxing kits (lnspiralis, Norwich, UK) were used.4 For standard reactions 0.5 μg supercoiled plasmid were mixed with 1 unit (~20.5 nM) *E. coli* topoisomerase IV in 1× reaction buffer (see kit manual) and incubated for 30 minutes at 37° C. The reactions were quenched by the addition of DNA gel loading buffer containing 10% (w/v) SDS. The samples were separated on 0.8% (w/v) agarose gels and DNA was visualized using Roti-GelStain (Carl Roth).

[0321] Following natural product concentrations were used in the assay:

[0322] Cystobactamide A: 815.8 μM; 163 μM; 80 μM, 16 μM; 8 μM; 1.6 μM; 0.8 μM; 0.16 μM; 0.08 μM; 0.016 μM

[0323] Cystobactamide A1: 543.5 μM; 108.7 μM; 54 μM; 10.8 μM; 5.4 μM; 1.087 μM; 0.54 μM; 0.108 μM; 0.054 μM; 0.0108 μM

[0324] Cystobactamide C: 300 μM; 60 μM; 30 μM; 6 μM; 3 μM; 0.6 μM; 0.3 μM; 0.06 μM; 0.03 μM; 0.006 μM

[0325] Cystobactamide D: 347 μM; 173.5 μM; 86.75 μM; 43.38 μM; 21.69 μM; 10.84 μM; 5.42 μM; 2.71 μM; 1.36 μM; 0.68 μM; 0.34 μM; 0.17 μM; 0.085 μM; 0.042 μM; 0.021 μM; 0.0106 μM; 0.0053 μM

[0326] Control reactions were: no enzyme and a standard reaction in presence of 5% (v/v) DMSO. All reaction samples were equilibrated for 10 minutes at room-temperature in the absence of DNA. Then the relaxed plasmid was added to start the reaction.

Topoisomerase II Relaxation Assay

[0327] To test the anti-topoisomerase II activity of cystobactamides, commercial human topoisomerase IV relaxing kits (Inspiralis, Norwich, UK) were used.4 For standard reactions 0.5 μg supercoiled plasmid were mixed with 1 unit (~20.5 nM) *E. coli* topoisomerase II in 1× reaction buffer (see kit manual) and incubated for 30 minutes at 37° C. The reactions were quenched by the addition of DNA gel loading buffer containing 10% (w/v) SDS. The samples were separated on 0.8% (w/v) agarose gels and DNA was visualized using Roti-GelStain (Carl Roth).

[0328] Following natural product concentrations were used in the assay:

[0329] Cystobactamide A: 815.8 μM; 163 μM; 80 μM, 16 μM; 8 μM; 1.6 μM; 0.8 μM; 0.16 μM; 0.08 μM; 0.016 μM

[0330] Cystobactamide A1: 543.5 μM; 108.7 μM; 54 μM; 10.8 μM; 5.4 μM; 1.087 μM; 0.54 μM; 0.108 μM; 0.054 μM; 0.0108 μM

[0331] Cystobactamide C: 300 μM; 60 μM; 30 μM; 6 μM; 3 μM; 0.6 μM; 0.3 μM; 0.06 μM; 0.03 μM; 0.006 μM

[0332] Cystobactamide D: 347 μM; 173.5 μM; 86.75 μM; 43.38 μM; 21.69 μM; 10.84 μM; 5.42 μM; 2.71 μM; 1.36 μM; 0.68 μM; 0.34 μM; 0.17 μM; 0.085 μM; 0.042 μM; 0.021 μM; 0.0106 μM; 0.0053 μM

[0333] Control reactions were: no enzyme and a standard reaction in presence of 5% (v/v) DMSO. All reaction samples were equilibrated for 10 minutes at room-temperature in the absence of DNA. Then the relaxed plasmid was added to start the reaction.

Topoisomerase I Relaxation Assay

[0334] To test the anti-topoisomerase II activity of cystobactamides, commercial *H. sapiens* topoisomerase I relaxing kits (Inspiralis, Norwich, UK) were used.4 For standard reactions 0.5 μg supercoiled plasmid were mixed with 1 unit (~20.5 nM) *H. sapiens* topoisomerase I in 1× reaction buffer (see kit manual) and incubated for 30 minutes at 37° C. The reactions were quenched by the addition of DNA gel loading buffer containing 10% (w/v) SDS. The samples were separated on 0.8% (w/v) agarose gels and DNA was visualized using Roti-GelStain (Carl Roth).

[0335] Following natural product concentrations were used in the assay:

[0336] Cystobactamide A: 815 μM; 81.5 μM; 8.15 μM

[0337] Cystobactamide A1: 543 μM; 54.3 μM; 5.43 μM

[0338] Cystobactamide C: 300 μM; 30 μM; 3 μM

[0339] Cystobactamide D: 277 μM; 27.2 μM; 2.77 μM

[0340] Control reactions were: no enzyme and a standard reaction in presence of 5% (v/v) DMSO. All reaction samples were equilibrated for 10 minutes at room-temperature in the absence of DNA. Then the relaxed plasmid was added to start the reaction

Quantification and Analysis

[0341] To determine IC50 values, the formation of supercoiled (gyrase) or relaxed (topoisomerase I, II IV) plasmid was quantified using Adobe Photoshop (Histogram mode). Plotting of these values versus the compound concentration yielded sigmoidal shaped curves, which were fitted using Hill's equation (Origin Pro 8.5). All determined IC50 values are the averages of three independent experiments.

REFERENCES

[0342] [1] T. Gruger, J. L. Nitiss, A. Maxwell, E. L. Zechiedrich, P. Heisig, S. Seeber, Y. Pommier, D. Strumberg, *Antimicrob. Agents Chemother.* 48, 2004, 4495-4504.

[0343] [2] H. Schedletzky, B. Wiedemann, P. Heisig, *J. Antimicrob. Chemother.* 43, 1999, 31-37.

[0344] [3] A. B. Khodursky, E. L. Zechiedrich, N. R. Cozzarelli, *Proc. Natl. Acad. Sci. USA* 92, 1995, 11801-11805.

[0345] [4] A. Schulte, P. Heisig, *J. Antimicrob. Chemother.* 46, 2000, 1037-1046.

[0346] [5] D. Keeney, A. Ruzin, F. McAleese, E. Murphy, P. A. Bradford, *J. Antimicrob. Chemother.* 61, 2008, 46-53.

[0347] [6] P. Heisig, H. Schedletzky, H. Falkenstein-Paul, *Antimicrob. Agents Chemother.* 37, 1993, 669-701.

[0348] [7] T. Mosmann, *J. Immunol. Meth.* 65, 1983, 55-63.

[0349] [8] Pommier, Y.; Leo, E.; Zhang, H.; Marchand, C. *Chemistry & Biology* 2010, 17, 421.

Synthesis of Cystobactamide A and C

[0350] First, the synthesis of cystobactamide C is described which can further be elaborated to the other cystobactamides.

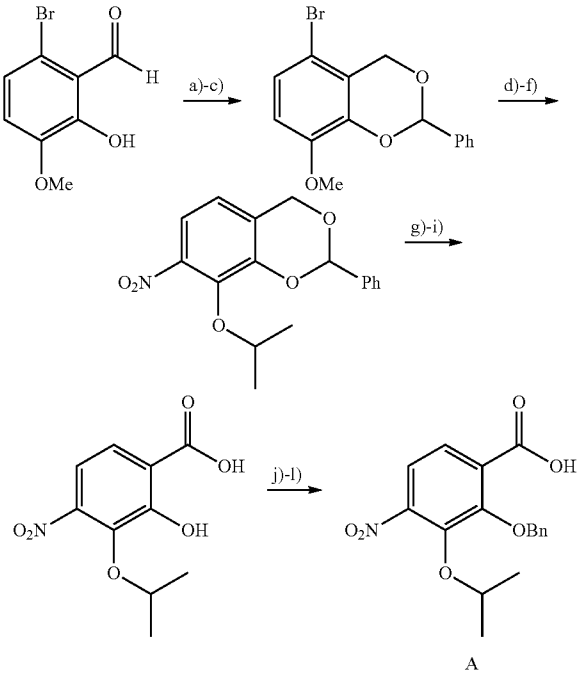
1.1. Cystobactamide C

[0351] The following Schemes 1 and 2 provide an overview on the synthesis of individual aromatic building blocks followed by assembling these to generate cystobactamide C.

[0352] Alternatively, step e) in Scheme 1 can be modified by using another alcohol (R'OH) instead of ^{i}PrOH. If for example EtOH is used, building blocks of cystobactamide H can be prepared. The same applies for step b) in the second reaction sequence given in Scheme 1. Here, also ^{i}PrOH can be exchanged by any other alcohol (R'OH). If for example MeOH is used, building blocks of cystobactamides C, G and H can be prepared. For the preparation of cystobactamide F, p-amino-benzoic acid derivatives such as p-aminobenzoic acid or corresponding N-protected aminobenzoic acid derivatives and p-nitrobenzoic acids are employed instead of building block B.

Scheme 1: Syntheses of arenes A and B followed by amide coupling.

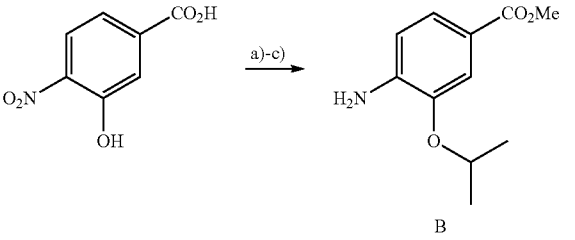
(central aromatic moiety)



a) BBr_3, CH_2Cl_2, -40° C.-rt, 17 h (95%); b) $NaBH_4$, THF, -40° C.-rt, 30 min (91%); c) $PhCH(OMe)_2$, pTSA•H_2O, THF, rt, 5 days (56%); d) $Ni(NO_3)_2$•$5H_2O$, pTsOH•H_2O, acetone, rt, 2.5 h (74%); e) ^{i}PrOH, DEAD, PPh_3, THF, rt, 17 h (85%); f) $Pd_2(dba)_3$, $(PhO)_3P$, ^{i}PrOH, dioxane, 80° C., 1.5 h (70%); g) Camphor-10-sulfonic acid, CH_2Cl_2/MeOH (1:2), 0° C.-rt, 17 h (90%); h) MnO_2, CH_2Cl_2, rt, 17 h (81%); i) 2-methyl-2-butene, $NaClO_2$/NaH_2PO_4, ^{t}BuOH, rt, 17 h (75%); j) $TMSCHN_2$, MeOH/PHMe, 0° C.-rt, 30 min (57%); k) BnOH, DEAD, PPh_3, THF, rt, 17 h (90%); l) LiOH, THF/H_2O (1:1), rt, 17 h (99%).

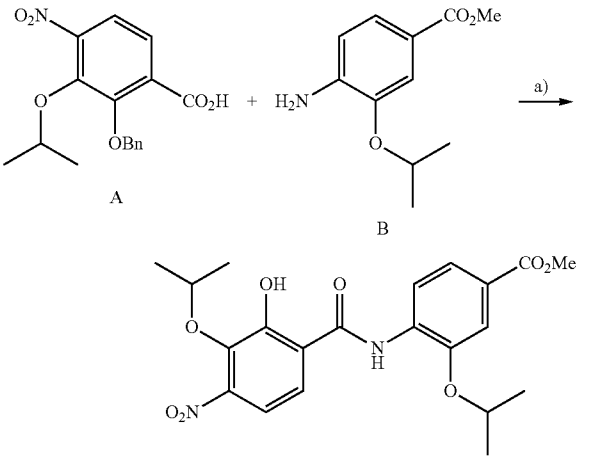
(terminal trisubstituted aromatic moiety)

-continued



a) $TMSCHN_2$, MeOH/PhMe, 0° C.-rt, 30 min (90%); b) ^{i}PrOH, DEAD, THF, rt, 17 h (quant); c) Pd/C, MeOH, H_2 atm., rt, 17 h (quant).

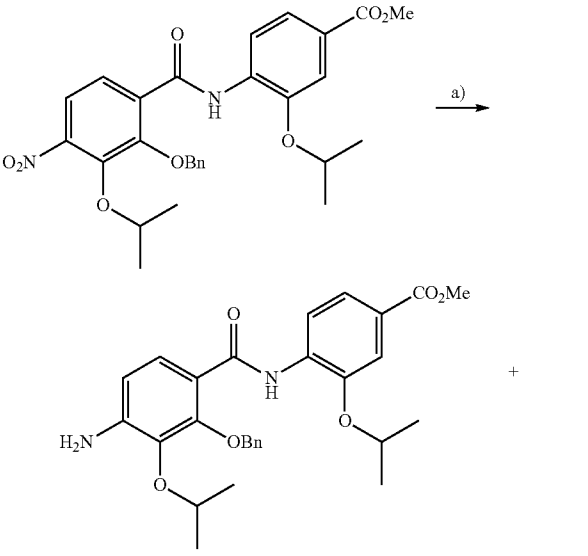
(merging aromatic moieties A and B)



a) I. A, Goshez's reagent, CH_2Cl_2, 40° C., 3 h; II. B, DIPEA, CH_2Cl_2, rt, 10 min, then I., 40° C., 2 days (68%)

Scheme 2: Finalization of cystobactamide C synthesis.

Cystobactamide C (finalization of synthesis)



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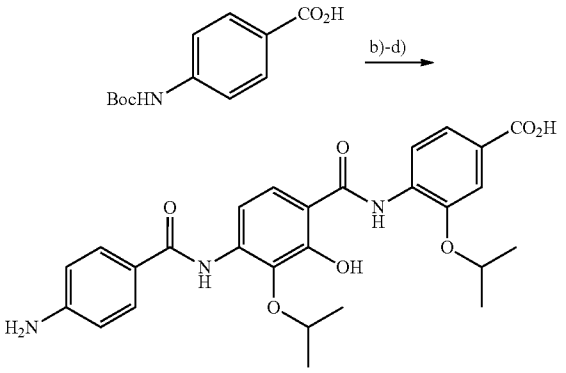


Cystobactamide C

a) Pd/C, MeOH, H_2 atm., rt, 3 h (96%); b) I. 4-Boc aminobenzoic acid, Goshez's reagent, CH_2Cl_2, rt, 1 h; II. B. DIPEA, CH_2Cl_2; then I., rt, 1 day (72%); c) TFA/CH_2Cl_2 (10:1), rt, 17 h (quant.); d) LiOH, THF/H_2O (1:1), rt, 17 h (99%).

1.2 Cystobactamide A

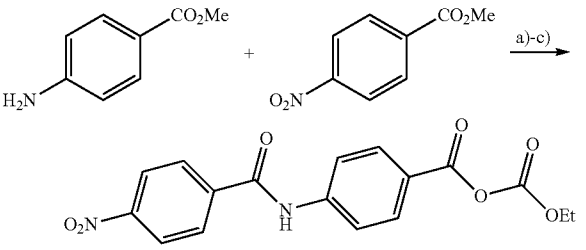
[0353] The more complex cystobactamides consist of the bisamide that represents cystobactamide C, a bisarylamide (fragment C) and a chiral linker element. In this section fragment C and the chiral linker element are reported first which is followed by the assembling of all three elements to provide cystobactamide A.

1.2.1 Synthesis of Bisarene C.

[0354]

Scheme 3: Synthesis of activated fragment C.

Fragment C



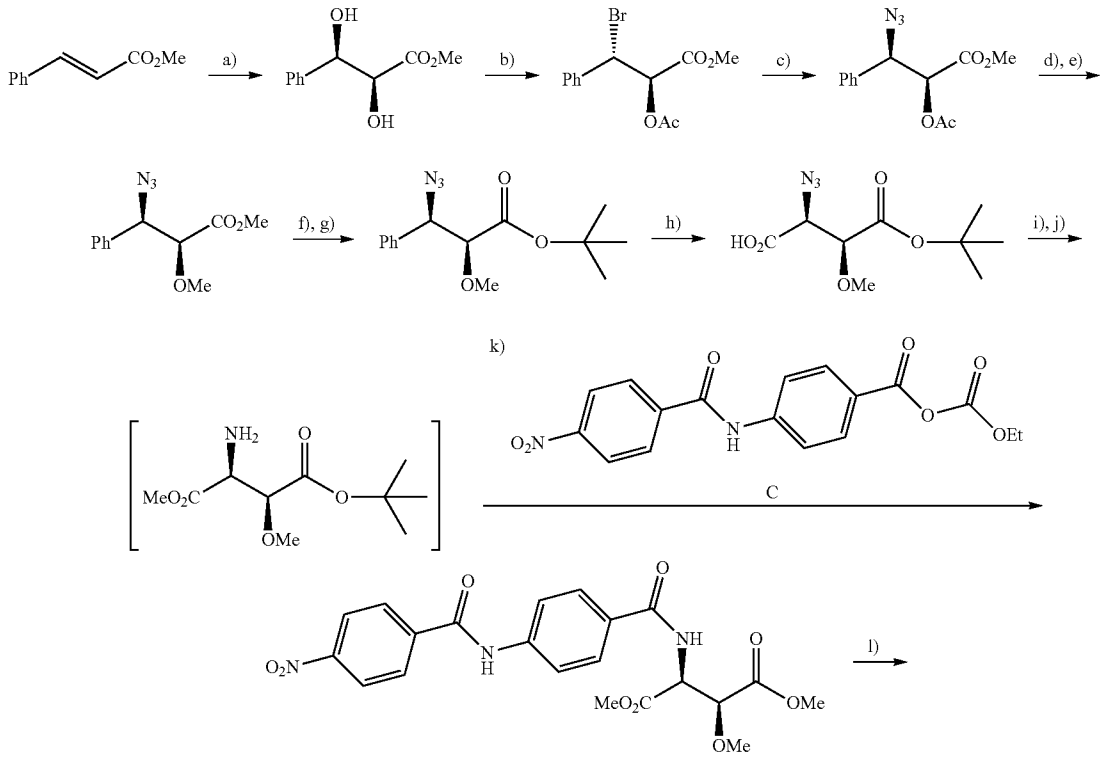
C

a) $P(OMe)_3$, I_2, THF, 3 days (75%); b) LiOH, THF/H_2O (1:1), rt, 17 h (80%); c) ethyl chloroformate, Et_3N, CH_3CN, 0° C. 30 min (67%).

1.2.2 Synthesis of the Chiral Building Block D with Bisarene C Attached

[0355] The synthesis starts from methyl cinnamate and chirality is introduced by the Sharpless asymmetric dihydroxylation. The phenyl ring serves as protecting group for the second carboxylate which is oxidatively liberated. Finally, building block C is attached to the free amino group. The corresponding enantiomeric fragment (ent)-D was prepared using AD mix α instead of AD mix β.

Scheme 4: Synthesis of carboxylic acid D starting from methylcinnamate.



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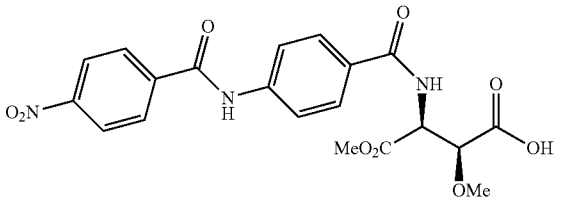
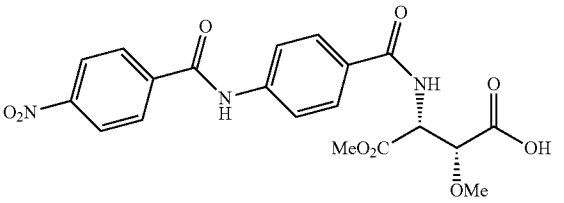


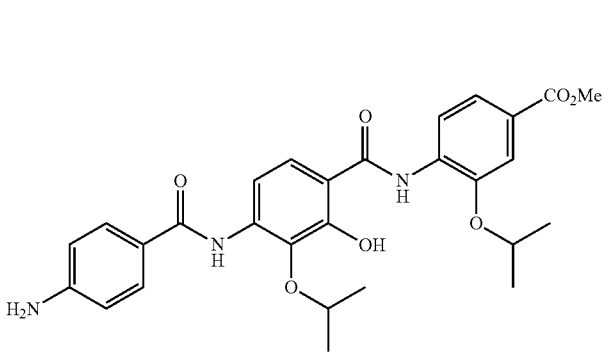
D



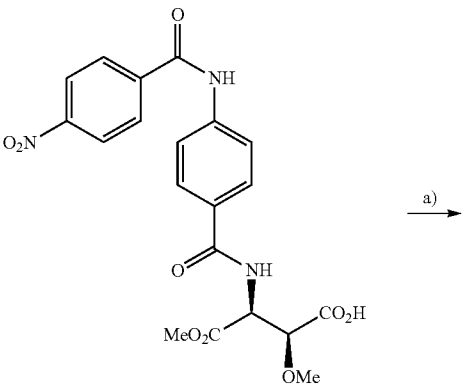
ent-D

a) AD mix β, $MeSO_2NH_2$, tBuOH/H_2O (1:1), 0° C., 12 h, then 25° C., 12 h, (79%, ee > 99%); b) 33% HBr/HOAc, 45° C., 30 min,. (71%); c) NaN_3, DMF, 25° C., 3 h, then 40° C., 2 h (89%); d) KOH, THF/H_2O; e) 2. MeI, Ag_2O, $CaSO_4$ (74% for two steps); f) KOH, THF/H_2O; g)Me_2N—CH($OtBu)_2$, toluene, 80° C. (87% for two steps); h) $RuCl_3$•H_2O, $NaIO_4$, $CHCl_3$/CH030CN/H_2O, 70° C.; i) MeI, Ag_2O, $CaSO_4$; j) Ph_3P, THF/H_2O, 50° C., k) DMF (16% for four steps); l) CF_3CO_2H, CH_2Cl_2, (quant).

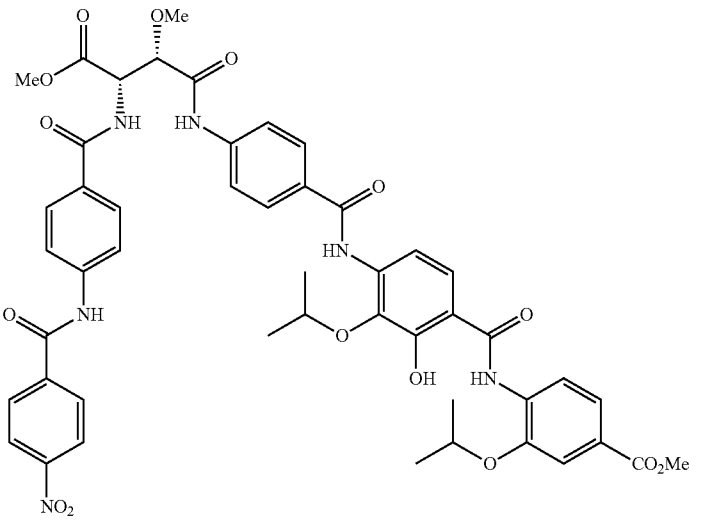
Scheme 5: Finalization of cystobactamide A synthesis.



Cystobactamide A (finalization of synthesis)



(Fragment A + Fragment B)



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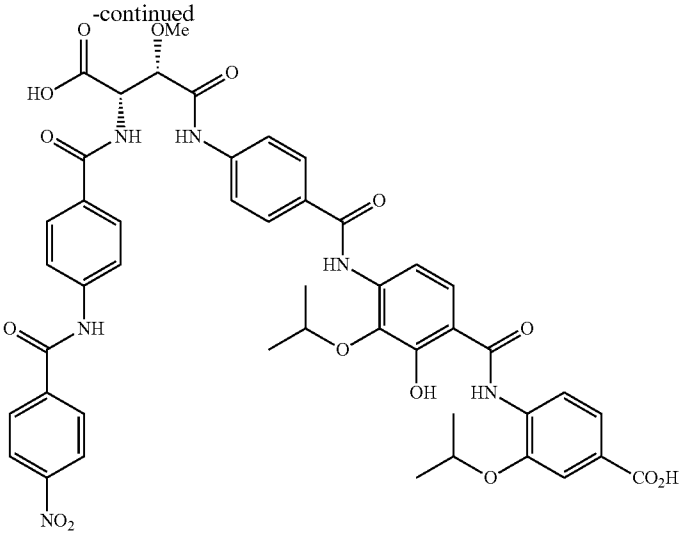


Cystobactamide A

a) HOAt, EDC•HCl, DIPEA, CH_2Cl_2, rt, 17 h (75%); b) LiOH, THF/H_2O(1/1), rt, (95%).

2. EXPERIMENTALS

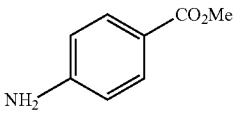
2.1 General Experimental Information

[0356] All reactions were performed in oven dried glassware under an atmosphere of nitrogen gas unless otherwise stated. ^{1}H-NMR spectra were recorded at 400 MHz with a Bruker AVS-400 or at 500 MHz with a Bruker DRX-500. ^{13}C-NMR spectra were recorded at 100 MHz with a Bruker AVS-400 and at 125 MHz with a Bruker DRX-500. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. Chemical shift values of ^{1}H and ^{13}C NMR spectra are commonly reported as values in ppm relative to residual solvent signal as internal standard. The multiplicities refer to the resonances in the off-resonance decoupled spectra. These were elucidated using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are reported using the following abbreviations: s=singlet (due to quaternary carbon), d=doublet (methine), t=triplet (methylene), q=quartet (methyl). Mass spectra (EI) were obtained at 70 eV with a type VG Autospec spectrometer (Micromass), with a type LCT (ESI) (Micromass) or with a type Q-TOF (Micromass) spectrometer in combination with a Waters Aquity Ultraperformance LC system. Analytical thin-layer chromatography was performed using precoated silica gel 60 F_{254} plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm or alternatively by staining with potassium permanganate, phosphomolybdic acid, 2,4-dinitrophenol or p-anisaldehyde solutions. Tetrahydrofuran (THF) was distilled under nitrogen from sodium/benzophenone. Dichloromethane (CH_2Cl_2) was dried using a Solvent Purification System (SPS). Commercially available reagents were used as supplied. Preparative high performance liquid chromatography using a Merck Hitachi LaChrom system (pump L-7150, interface D-7000, diode array detector L-7450 (A=220-400 nm, preferred monitoring at λ=230 nm)) with column (abbreviation referred to in the experimental part given in parentheses): Trentec Reprosil-Pur 120 C18 AQ 5 μm, 250×8 mm, with guard column, 40×8 mm (C18-SP). Flash column chromatography was performed on Merck silica gel 60 (230-400 mesh). Eluents used for flash chromatography were distilled prior to use. Melting points were measured using a SRS OptiMelt apparatus. Optical rotations [α] were measured on a Polarimeter 341 (Perkin Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}.

2.2 Specific Procedures

4-Aminomethylbenzoate

[0357]



[0358] MeOH (200 mL) was provided in a flask and acetyl chloride (2.6 mL, 36.5 mmol, 1 eq) was slowly added. Then 4-aminobenzoic acid (5.00 g, 36.5 mmol) was added and the solution was stirred 7 days at room temperature. The solvent was removed under reduced pressure and 4-aminomethylbenzoate (5.38 g, 35.59 mmol, quantitative) was obtained as a beige solid.

[0359] The titled compound decomposes before reaching its melting point.

[0360] ATR-IR (neat): ũ=2828, 2015, 1724, 1612, 1558, 1508, 1430, 1316, 1280, 1181, 1109, 1072, 1022, 984, 959, 853, 786, 757, 686, 653 cm^{-1}.

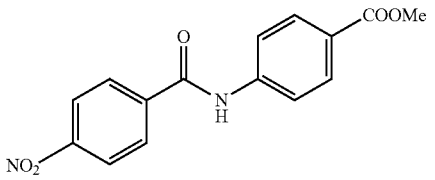
[0361] ^{1}H-NMR (400 MHz, CD_3OD): δ 8.19-8.13 (m, 2H), 7.53-7.48 (m, 2H), 3.93 (s, 3H) ppm.

[0362] ^{13}C-NMR (100 MHz, CD_3OD): δ 167.2 137.0, 132. 4, 131.7, 124.2, 53.0 ppm

[0363] HRMS (ESI): Calculated for $C_8H_{10}NO_2$ $(M+H)^+$: 152.0712. found: 152.0706.

4-(4-Nitrobenzamido)methyl benzoate

[0364]



[0365] A solution of $P(OMe)_3$ (3.5 mL, 29.8 mmol) in CH_2Cl_2 (100 mL) was cooled with an ice bath, then I_2 (7.56 g, 29.8 mmol) was added. After the solid iodine was completely dissolved, p-nitrobenzoic acid (5.52 g, 29.8 mmol) and Et_3N (4.70 mL, 33.7 mmol) were added in sequential order, and the solution was stirred for 10 minutes in a cooling bath. 4-aminomethylbenzoate (3.00 gr, 19.9 mmol) was added and the mixture was stirred for 10 minutes. After removing the cooling bath, the reaction mixture was stirred for 3 days at room temperature, then diluted with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3×). The combined, organic layer was sequentially washed with H_2O, 1 M HCl, H_2O, and brine. The combined organic layers were dried with anhydrous $MgSO_4$ and the solvent concentrated in vacuo, yielding the title compound (4.4 g, 14.65 mmol, 75%) as a beige solid. mp: 245-246° C.

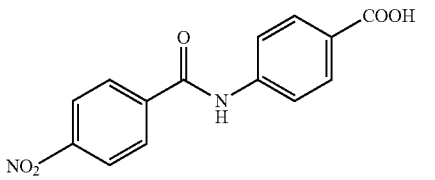
[0366] ^1H NMR (400 MHz, DMSO) δ 10.87 (s, $1H_{NH}$), 8.39 (d, J=8.8 Hz, 2H), 8.20 (d, J=8.8 Hz, 2H), 7.99 (d, J=8.8 Hz, 2H), 7.95 (d, J=8.8 Hz, 2H), 3.84 (s, $3H_{OMe}$) ppm.

[0367] ^{13}C NMR (100 MHz, DMSO) δ 166.2, 164.9, 149.77, 143.6, 140.7, 130.7, 129.8, 125.3, 124.2, 120.2, 52.4 ppm.

[0368] HRMS (ESI): Calculated for $C_{15}H_{13}N_2O_2Na$ $(M+H)^+$: 301.0824. found: 301.0828.

4-(4-Nitrobenzamido)benzoate

[0369]



[0370] 4-(4-Nitrobenzamido)methyl benzoate (4.32 g, 14.38 mmol) was dissolved in a mixture 1/1 of THF/H_2O (77/77 mL). Then, solid LiOH (5.16 g, 215.66 mmol) was added and the system was stirred at room temperature for 17 hours. 1M HCl was added until pH-1 and the resulting solid was filtered and dried in vacuo. The title compound (3.3 g, 11.54 mmol, 80%) was obtained as a pale yellow solid. mp: 322-324° C.

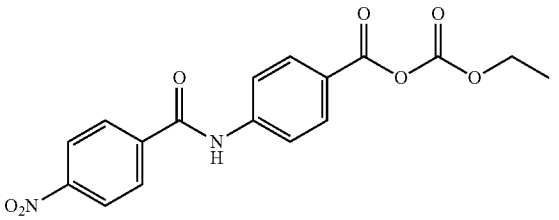
[0371] ^1H NMR (400 MHz, C_6D_6) δ 10.83 (s, $1H_{CO2H}$), 8.34 (d, J=8.6 Hz, 1H), 8.29 (d, J=8.6 Hz, 1H), 8.13 (d, J=8.6 Hz, 1H), 8.06 (d, J=8.6 Hz, 1H), 7.75 (s, $1H_{NH}$) ppm.

[0372] ^{13}C NMR (100 MHz, C_6D_6) δ 168.2, 164.6, 162.2, 149.7, 143.9, 141.1, 131.1, 129.8, 123.5, 120.4 ppm.

[0373] HRMS (ESI): Calculated for $C_{14}H_9N_2O_5(M-H)^-$: 285.0511. found: 285.0506.

(Ethyl carbonic) 4-(4-nitrobenzamido)benzoic anhydride

[0374]



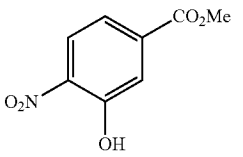
[0375] To a stirred solution of 4-aminobenzoic acid (1.5 g, 10.9 mmol) and N, N-dimethylaniline (2.0 g, 10.9 mmol) in acetone was added 4-nitrobenzoyl chloride at 0° C. Then, the reaction mixture was allowed to warm to room temperature and stirred for another hour. The resulting solid was filtered and purified by recrystallization in DMF to afford 4-(4-nitrobenzoylamino)-benzoic acid (2.75 g, 88%).

[0376] 4-(4-Nitro-benzoylamino)-benzoic acid (0.6 g, 2.1 mmol) was dissolved in 14 ml CH_3CN. Then Et_3N (0.31 ml, 2.2 mmol) was added at 0° C. To this resulting solution ethyl chloroformate was added. After stirring for 30 min at 0° C., the white precipitate was filtered and washed with cold CH_3CN, then dried under high vacuum at room temperature to afford the title anhydride 0.5 g, 67%.

[0377] ^1H-NMR (400 MHz, DMSO, DMSO=2.50 ppm): δ=1.33 (dd, J=7.2 Hz, 3H), 4.37 (q, J=7.2 Hz, 2H), 8.02-8.09 (m, 4H), 8.21 (d, J=8.8 Hz, 2H), 8.40 (d, J=8.8 Hz, 2H), 11.01 (s, 1H).

3-Hydroxy-4-nitromethylbenzoate

[0378]



[0379] $TMSCHN_2$ (2.0 M in Et_2O, 13.20 mL, 26.48 mmol) was added to a solution of 3-hydroxy-2-nitrobenzoic acid (2.50 g, 13.65 mmol) in a mixture of toluene/methanol (81/36 mL) at 0° C. After stirring at 0° C. for 30 minutes, the solvent was evaporated in vacuo to give an oily residue, which was purified by flash chromatography (petroleum ether/ethyl acetate=9:1) to yield the title compound (2.43 g, 12.33 mmol, 90%) as a yellow solid.

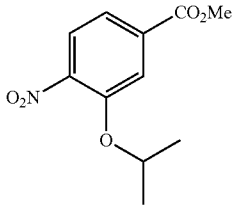
[0380] mp: 91-92° C.

[0381] ^1H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, $1H_{\_OH}$), 8.17 (d, J=8.8 Hz, 1H), 7.83 (d, J=1.8 Hz, 1H), 7.61 (dd, J=8.8, 1.8 Hz, 1H), 3.96 (s, 3H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$) δ 165.0, 154.8, 138.1, 125.4, 121.8, 120.74, 53.1 ppm. HRMS (ESI): Calculated for $C_8H_6NO_5$ $(M-H)^-$: 196.0246. found: 196.0249.

3-Isopropoxy-4-nitromethylbenzoate

[0382]



[0383] 3-Hydroxy-4-nitromethylbenzoate (2.30 g, 10.89 mmol) was dissolved in THF (100 mL). ^{i}PrOH (1.10 mL, 14.16 mmol) and PPh_3 (3.90 g, 14.70 mmol) were added, and the mixture was stirred until all components were dissolved. DEAD (2.2 M in toluene, 14.16 mmol, 6.50 mL) was added and the mixture was stirred at room temperature 17 hours. The solvent was evaporated in vacuo to give an oily residue, which was purified by flash chromatography (petroleum ether/ethyl acetate=95:5) to yield the title compound (2.61 g, 10.91 mmol, quantitative) as a yellow oil.

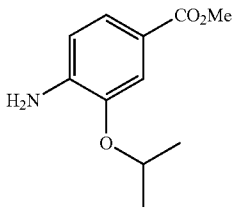
[0384] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J=8.4 Hz, 2H), 7.64 (dd, J=8.3, 1.6 Hz, 1H), 4.77 (hept, J=6.1 Hz, 1H), 3.95 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H) ppm.

[0385] ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 150.9, 134.6, 125.2, 121.2, 117.1, 73.2, 52.9, 21.9 ppm.

[0386] HRMS (Qtof): Calculated for $C_8H_6NO_5$ $(M+Na)^+$: 262.0691. found: 262.0700.

3-Isopropoxy-4-aminomethylbenzoate

[0387]



[0388] 3-Isopropoxy-4-nitromethylbenzoate (2.60 g, 10.87 mmol) was dissolved in MeOH (91.0 mL) and degassed. Pd/C (10% wt., 0.58 g, 0.54 mmol) was added and vacuum was applied under cooling to remove air. The flask was flushed with H_2 and the suspension was stirred for 17 hours at room temperature. The catalyst was filtered over Celite®, washed with MeOH and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc=7/3). 3-Isopropoxy-4-aminomethylbenzoate was obtained (2.27 g, 10.85 mmol, quantitative) as a light orange solid.

[0389] mp: 55-57° C.

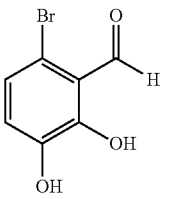
[0390] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J=8.2, 1.7 Hz, 1H), 7.46 (d, J=1.7 Hz, 1H), 6.66 (dd, J=8.2, 5.1 Hz, 1H), 4.63 (sept, J=5.1 Hz, 1H), 3.85 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H) ppm.

[0391] ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 144.24, 142.3, 124.0, 119.5, 114.1, 113.5, 70.9, 51.8, 22.3 ppm.

[0392] HRMS (ESI): Calculated for $C_{11}H_{16}NO_3$ $(M+H)^+$: 210.1130. found: 210.1126.

6-Bromo-2,3-dihydroxybenzaldehyde

[0393]



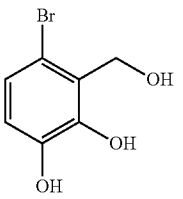
[0394] To a solution of 6-bromo-2-hydroxy-3-methoxybenzaldehyde (25.0 g, 108.2 mmol) in CH_2Cl_2 (270 mL) at −30° C. was slowly added BBr_3 (1 M in CH_2Cl_2, 200.0 mL, 200.0 mmol) via additional funnel over a period of 45 minutes. The solution was allowed to warm to room temperature and stirred 17 hours. H_2O was added and the reaction mixture was stirred for additional 30 minutes. The solution was then extracted with EtOAc (3×) and washed with H_2O. The combined, organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give the title compound (22.16 g, 102.11 mmol, 95%) as a yellow solid. mp: 135-136° C.

[0395] ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (d, J=0.5 Hz, 1H$_{_OH}$), 10.27 (s, 1H$_{_CHO}$), 7.07 (d, J=8.5 Hz, 1H), 7.02 (dd, J=8.5, 0.5 Hz, 1H), 5.67 (s, 1H$_{_OH}$) ppm.

[0396] ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 151.2, 145.0, 124.4, 122.0, 117.5, 116.1 ppm. HRMS (ESI): Calculated for $C_7H_4BrO_3$ $(M-H)^-$: 214.3943. found: 214.9344.

4-Bromo-3-hydroxymethylbenzene-1,2-diol

[0397]



[0398] A solution of 6-bromo-2,3-dihydroxybenzaldehyde (22.16 g, 102.10 mmol) in THF (650 mL) at −40° C. was treated with $NaBH_4$ (3.86 g, 102.10 mmol) portion wise (3×). The resulting mixture was stirred for 30 minutes at room temperature. A saturated aqueous solution of NH_4Cl was added and the mixture was stirred for another 10 minutes, before being finally treated with 1M HCl. After 10 minutes of additional stirring, the aqueous phase was extracted with EtOAc (3×). The combined, organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvent was removed

under reduced pressure to yield the title compound (20.27 g, 92.53 mmol, 91%) as a colorless solid.

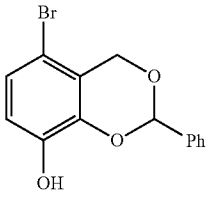
[0399] mp: 90-92° C.

[0400] ^{1}H NMR (400 MHz, MeOD) δ 6.88 (d, J=8.5 Hz, 1H), 6.64 (d, J=8.5 Hz, 1H), 4.82 (s, 2H) ppm.

[0401] ^{13}C NMR (100 MHz, MeOD) δ 147.1, 146.1, 126.9, 123.9, 116.6, 114.4, 61.1 ppm. HRMS (ESI): Calculated for $C_7H_6BrO_3$ $(M-H)^-$: 216.9500. found: 216.9505.

5-Bromo-2-phenyl-4H-benzo-[1,3]-dioxin-8-ol

[0402]



[0403] A solution of 4-bromo-3-hydroxymethylbenzene-1, 2-diol (20.27 g, 92.53 mmol) in THF (550 mL) was treated with $PhCH(OMe)_2$ (20.8 mL, 138.8 mmol) and $pTSA.H_2O$ (0.19 g, 1.02 mmol). The mixture was stirred at room temperature for 5 days. CH_2Cl_2 was added and then washed successively with 5% aqueous $NaHCO_3$ and brine. The aqueous phase was extracted with EtOAc (3×). The combined, organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash chromatography (petroleum ether/EtOAc=95/5) afforded 5-bromo-2-phenyl-4H-benzo-[1,3]-dioxin-8-ol (16.02 g, 52.16 mmol, 56%) as a colorless solid.

[0404] mp: 89-91° C.

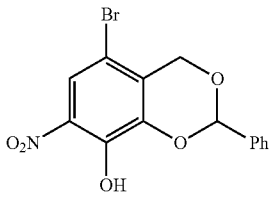
[0405] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (m, 2H), 7.50-7.43 (m, 3H), 7.07 (d, J=8.6 Hz, 1H), 6.78 (d, J=8.6 Hz, 1H), 5.97 (s, 1H), 5.40 (s, 1H$_{OH}$), 4.99 (s, 2H) ppm.

[0406] ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 141.8, 136.1, 130.1, 128.8, 126.7, 124.9, 121.0, 115.0, 109.4, 100.0, 67.8 ppm.

[0407] HRMS (ESI): Calculated for $C_{14}H_{10}BrO_3$ $(M-H)^-$: 304.9813. found: 304.9813.

5-Bromo-7-nitro-2-phenyl-4H-benzo-[1,3]-dioxin-8-ol

[0408]



[0409] 5-Bromo-2-phenyl-4H-benzo-[1,3]-dioxin-8-ol (6.00 g, 19.54 mmol; max. amount) was dissolved in acetone (250 mL). Then, $Ni(NO_3)_2.5H_2O$ (5.68 g, 19.54 mmol) and $pTSA.H_2O$ (3.72 g, 19.54 mmol) were added. The mixture was stirred at room temperature for 2.5 h. The reaction mixture was filtered over Celite®, washed with CH_2Cl_2 and concentrated in vacuo. Purification by flash chromatography (dry load: SiO_2+CH_2Cl_2; petroleum ether/ethyl acetate=9:1) yielded the titel compound (5.08 g, 14.43 mmol, 74%) as a bright yellow solid.

[0410] mp: 154-156° C.

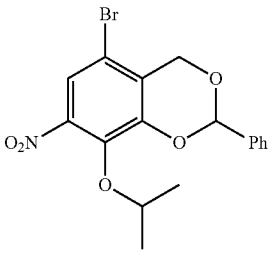
[0411] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H$_{OH}$), 7.96 (s, 1H), 7.65-7.57 (m, 2H), 7.48-7.42 (m, 3H), 6.02 (s, 1H), 4.99 (s, 2H) ppm.

[0412] ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 135.5, 133.2, 130.2, 129.0, 128.9, 126.7, 119.2, 109.2, 99.9, 67.4 ppm.

[0413] HRMS (ESI): Calculated for $C_{14}H_9BrNO_5$ $(M-H)^-$: 359.9664. found: 349.9660.

5-Bromo-8-isopropoxy-7-nitro-2-phenyl-4H-benzo-[1,3]-dioxine

[0414]



[0415] 5-Bromo-7-nitro-2-phenyl-4H-benzo-[1,3]-dioxin-8-ol (13.79 g, 39.16 mmol) was dissolved in THF (429 mL). iPrOH (4.00 mL, 50.91 mmol) and PPh_3 (13.87 g, 52.87 mmol) were added, and the mixture was stirred until all components were dissolved. DEAD (2.2 M in toluene, 23.1 mL, 50.91 mmol) was slowly added (via syringe pump) and the mixture was stirred at room temperature 17 hours. The solvent was evaporated in vacuo to give an oily residue, which was purified by flash chromatography (petroleum ether/ethyl acetate=96:4) to yield the title compound (13.08 g, 33.18 mmol, 85%) as a colorless solid.

[0416] mp: 87-89° C.

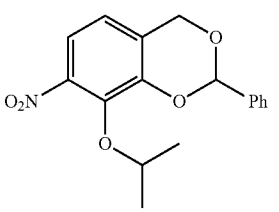
[0417] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.59-7.54 (m, 2H), 7.50-7.43 (m, 3H), 5.97 (s, 1H), 5.00 (s, 2H), 4.69 (hept, J=6.2 Hz, 1H), 1.31 (d, J=6.2 Hz, 3H), 1.28 (d, J=6.2 Hz, 3H) ppm.

[0418] ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 149.0, 144.5, 139.9, 135.7, 130.1, 128.8, 126.4, 126.2, 119.8, 112.7, 99.7, 78.1, 67.6, 22.6, 22.4 ppm.

[0419] HRMS (Qtof): Calculated for $C_{14}H_9BrNO_5$ $(M+Na)^+$: 416.0110. found: 416.0101.

8-Isopropoxy-7-nitro-2-phenyl-4H-benzo-[1,3]-dioxin, 73

[0420]



[0421] 5-Bromo-8-isopropoxy-7-nitro-2-phenyl-4H-benzo-[1,3]-dioxine 72 (4.00 g, 10.15 mmol), $Pd_2(dba)_3$ (0.93 g, 1.01 mmol), $(PhO)_3P$ (0.53 mL, 2.03 mmol), Cs_2CO_3 (4.30 g, 13.19 mmol) and ^iPrOH (4.7 mL, 60.88 mmol) were dissolved in 1,4-dioxane (28 mL). The oil bath was preheated to 60° C. and the mixture was stirred at 80° C. for 1.5 hours. The reaction mixture was filtered through Celite® and washed with EtOAc. The combined, organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash chromatography (petroleum ether/ethyl acetate=96:4) to yield the title compound (2.24 g, 7.10 mmol, 70%) as a pale yellow solid.

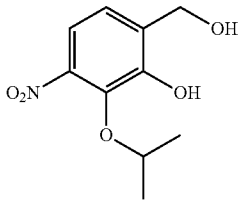
[0422] mp: 80-82° C.

[0423] ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.55 (m, 2H), 7.51-7.41 (m, 3H), 7.37 (d, J=8.5 Hz, 1H), 6.81 (d, J=8.5 Hz, 1H), 6.01 (s, 1H), 5.19 (d, J=15.5 Hz, 1H), 5.03 (d, J=15.5 Hz, 1H), 4.71 (hept, J=6.2 Hz, 1H), 1.32 (d, J=6.2 Hz, 3H), 1.28 (d, J=6.2 Hz, 3H) ppm.

[0424] ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.67, 144.27, 140.55, 136.26, 129.85, 128.72, 126.54, 126.34, 118.82, 116.69, 99.61, 77.71, 66.44, 22.65, 22.41 ppm. HRMS (QTof): Calculated for $C_{17}H_{17}NO_5Na$ $(M+Na)^+$: 338.1004. Found: 338.1003.

6-Hydroxymethyl-2-isopropoxy-3-nitrophenol

[0425]



[0426] To a mixture of 8-isopropoxy-7-nitro-2-phenyl-4H-benzo[1,3]-dioxine (4.24 g, 13.43 mmol) in MeOH (102 mL) and CH_2Cl_2 (42 mL) at 0° C. was added camphor sulfonic acid (3.12 g, 13.43 mmol). The mixture was stirred at room temperature for 17 hours. The reaction mixture was quenched with Et_3N until pH-8, concentrated in vacuo and purified by flash chromatography (petroleum ether/ethyl acetate=7:3) to yield the title compound (2.75 g, 12.09 mmol, 90%) as a brownish solid.

[0427] mp: 39-41° C.

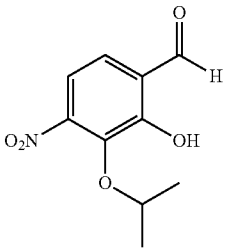
[0428] ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J=7.4 Hz, 1H), 7.12 (d, J=7.4 Hz, 1H), 6.61 (s, 1H$_{OH}$), 4.81 (d, J=3.5 Hz, 2H), 4.39 (hept, J=7.4 Hz, 1H), 1.36 (s, 3H), 1.35 (s, 3H) ppm.

[0429] ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.5, 132.4, 122.1, 116.5, 79.2, 61.3, 22.5 ppm.

[0430] HRMS (ESI): Calculated for $C_{10}H_{12}NO_5$ $(M-H)^-$: 226.0715. found: 226.0717.

2-Hydroxy-3-isopropoxy-4-nitrobenzaldehyde

[0431]



[0432] 6-Hydroxymethyl-2-isopropoxy-3-nitrophenol (2.97 g, 13.05 mmol) was dissolved in CH_2Cl_2 (58 mL). Then MnO_2 (11.35 g, 130.53 mmol) was added and the mixture was stirred at rt 17 h. The mixture was filtered over Celite® and washed with CH_2Cl_2. The solvent was concentrated to give the title compound (2.38 g, 10.57 mmol, 81%) as a brown oil.

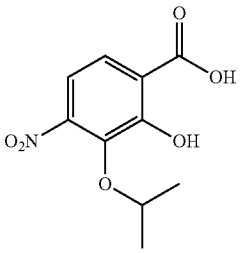
[0433] ^1H NMR (400 MHz, $CDCl_3$) δ 11.44 (s, 1H$_{CHO}$), 9.97 (s, 1H$_{OH}$), 7.39 (d, J=8.4 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H), 4.88 (hept, J=6.2 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H) ppm.

[0434] ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.39, 156.53, 149.36, 139.74, 127.28, 122.57, 114.32, 77.42, 77.16, 22.51. ppm.

[0435] HRMS (ESI): Calculated for $C_{10}H_{10}NO_5$ $(M-H)^-$: 224.0559. Found: 224.0535.

2-Hydroxy-3-isopropoxy-4-nitrobenzoic acid

[0436]



[0437] 2-Hydroxy-3-isopropoxy-4-nitrobenzaldehyde (2.36 g, 10.49 mmol) was dissolved in tert-buthanol (71 mL). 2-Methyl-2-butene (2M in THF, 36.7 mL, 73.45 mmol) and a solution of $NaClO_2$ (2.85 g, 31.48 mmol) and NaH_2PO_4 (6.32 g, 47.22 mmol) in H_2O (51 mL) were added in sequential order. The reaction mixture was stirred at room temperature for 17 hours. 6M NaOH was added until ph-10 and the solvent was concentrated in vacuo. H_2O was added and the organic layer was extracted with petroleum ether (2×). The aqueous layer was acidified with 6M HCl until pH-1 and extracted with ethyl acetate (3×). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was concentrated in vacuo to yield the title compound (1.90 g, 7.87 mmol, 75%) as a dark wax.

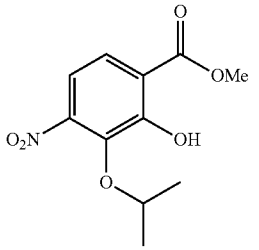
[0438] ^1H NMR (400 MHz, MeOD) δ 7.72 (d, J=8.7 Hz, 1H), 7.15 (d, J=8.7 Hz, 1H), 4.86-4.82 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H) ppm.

[0439] ^{13}C NMR (100 MHz, MeOD) δ 172.7, 158.0, 140.0, 125.8, 117.4, 113.8, 77.5, 22.6 ppm.

[0440] HRMS (ESI): Calculated for $C_{10}H_{10}NO_6$ $(M-H)^-$: 240.0508. found: 240.0510.

2-Hydroxy-3-isopropoxy-4-nitrobenzoate

[0441]



[0442] $TMSCHN_2$ (2.0 M in Et_2O, 0.87 mL, 1.75 mmol) was added to a solution of 2-hydroxy-3-isopropoxy-4-nitrobenzoic acid (0.32 g, 1.35 mmol) in a mixture of toluene/methanol (10.4/2 mL) at 0° C. After stirring at 0° C. for 30 minutes, the solvent was evaporated in vacuo to give an oily residue, which was purified by flash chromatography (SiO_2. Et_3N; petroleum ether/ethyl acetate=95:5) to yield the title compound (0.24 g, 0.94 mmol, 57%) as a yellow oil.

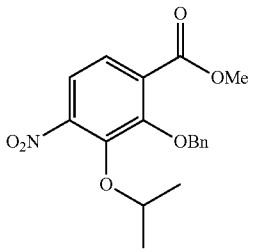
[0443] ^1H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H_OH), 7.63 (d, J=8.8 Hz, 1H), 7.12 (d, J=8.8 Hz, 1H), 4.84 (hept, J=6.2 Hz, 1H), 4.00 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H) ppm.

[0444] ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 188.9, 176.1, 170.0, 157.0, 149.2, 139.8, 123.9, 115.7, 113.4, 77.4, 53.2, 22.5 ppm.

[0445] HRMS (ESI): Calculated for $C_{11}H_{12}NO_6$ $(M-H)^-$: 254.0665. found: 254.0666.

2-Benzyloxy-3-isopropoxy-4-nitrobenzoate

[0446]



[0447] 2-Hydroxy-3-isopropoxy-4-nitrobenzoate (0.17 g, 0.69 mmol) was dissolved in THF (7.5 mL). BnOH (92.6 μL, 0.89 mmol) and PPh_3 (0.24 g, 0.93 mmol) were added, and the mixture was stirred until all components are dissolved. DEAD (2.2 M in toluene, 0.41 mL, 0.89 mmol) was slowly added (via syringe pump) and the mixture was stirred at room temperature 17 hours. The solvent was evaporated in vacuo to give an oily residue, which was purified by flash chromatography (petroleum ether/ethyl acetate=95:5) to yield the title compound (0.20 g, 0.58 mmol, 85%) as a colorless oil.

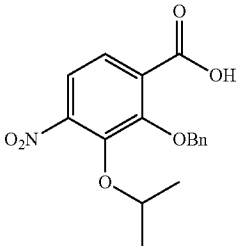
[0448] ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J=8.6 Hz, 1H), 7.50 (d, J=8.6 Hz, 1H), 7.48-7.44 (m, 2H), 7.42-7.35 (m, 3H), 5.14 (s, 2H), 4.74 (hept, J=6.2 Hz, 1H), 3.86 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H) ppm.

[0449] ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 153.4, 148.4, 145.7, 136.4, 130.9, 128.7, 128.7, 128.7, 125.1, 119.3, 78.2, 76.4, 52.8, 22.5 ppm.

[0450] HRMS (QTof): Calculated for $C_{18}H_{19}NO_6Na$ $(M+Na)^+$: 368.1110. found: 368.1112.

2-Benzyloxy-3-isopropoxy-4-nitrobenzoic acid

[0451]



[0452] 2-Benzyloxy-3-isopropoxy-4-nitrobenzoate (0.23 g, 0.67 mmol) was dissolved in a mixture 1/1 of THF/H_2O (3.5/3.5 mL). Then, solid LiOH (0.16 g, 6.67 mmol) was added and the reaction mixture was stirred at room temperature for 17 hours. The aqueous layer was acidified with 1M HCl until pH-1 and extracted with EtOAc (3×). The organic extracts were combined, dried over anhydrous $MgSO_4$ and filtered. The solvent was concentrated in vacuo to yield the title compound (0.21 g, 0.63 mmol, 95%) as a yellow wax.

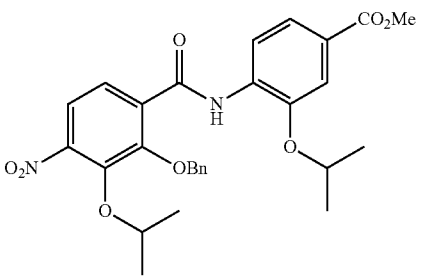
[0453] ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J=8.7 Hz, 1H), 7.58 (d, J=8.7 Hz, 1H), 7.41 (s, 5H), 5.35 (s, 2H), 4.71-4.62 (m, 1H), 1.36 (s, 3H), 1.35 (s, 3H) ppm.

[0454] ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 152.8, 149.7, 144.7, 134.1, 129.8, 129.4, 129.2, 126.98, 120.0, 79.1, 77.7, 22.5 ppm.

[0455] HRMS (ESI): Calculated for $C_{17}H_{16}NO_6$ $(M-H)^-$: 330.0978. found: 330.0976.

4-(2-(Benzyloxy)-3-isopropoxy-4-nitrobenzamido)-3-isopropoxybenzoate

[0456]



[0457] 2-Benzyloxy-3-isopropoxy-4-nitrobenzoic acid (51.5 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (8 mL) and preactivated with Ghosez's reagent (66.0 μL, 0.50 mmol) for 3 hours at 40° C. 3-Isopropoxy-4-aminomethylbenzoate (0.12 g, 0.55 mmol) was dissolved in CH_2Cl_2 (8 mL) and N,N-diisopropylethylamine (DIPEA) was added (0.20 mL, 1.12 mmol). The solution containing the acid chloride was then added and the reaction mixture stirred for 2 days at 40°

C. The solvent was then removed and the crude product was purified by preparative HPLC (RP-18; run time 100 min; H_2O/MeCN=100:0→0:100; tr=80 min) providing the title compound (56.9 mg, 0.11 mmol, 68%) as a light yellow oil.

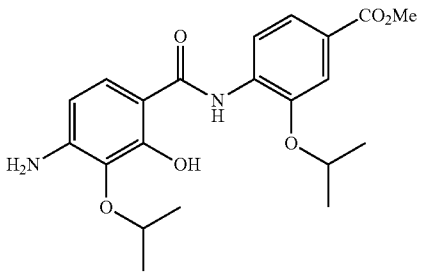
[0458] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H$_{_NH}$), 8.55 (d, J=8.5 Hz, 1H), 7.85 (d, J=8.7 Hz, 1H), 7.70 (dd, J=8.5, 1.7 Hz, 1H), 7.59 (d, J=8.7 Hz, 1H), 7.57 (d, J=1.7 Hz, 1H), 7.25-7.12 (m, 5H), 5.25 (s, 2H), 4.75-4.67 (m, 1H), 4.67-4.59 (m, 1H), 3.93 (s, 3H), 1.40 (d, J=6.2 Hz, 6H), 1.28 (d, J=6.0 Hz, 6H) ppm.

[0459] ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 161.4, 151.1, 147.9, 146.1, 145.2, 134.1, 132.9, 132.9, 130.0, 129.4, 128.7, 125.79, 125.6, 123.3, 120.1, 119.5, 113.3, 78.9, 77.4, 71.7, 52.3, 22.6, 22.1 ppm.

[0460] HRMS (ESI): Calculated for $C_{28}H_{31}N_2O_8$ $(M+H)^+$: 523.2080. found: 523.2075.

4-(4-Amino-2-hydroxy-3-isopropoxybenzamido)-3-isopropoxybenzoate

[0461]



[0462] 4-[2-(Benzyloxy)-3-isopropoxy-4-nitrobenzamido]-3-isopropoxy-benzoate (7.9 mg, 0.015 mmol) was dissolved in MeOH (0.5 mL) and degassed. Pd/C (10% wt., 2 mg, 0.0014 mmol) was added and vacuum was applied under cooling to remove air. The flask was flushed with H_2 and the suspension was stirred for 3 hours at room temperature. The catalyst was filtered off over Celite®, washed with MeOH and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate=7:3) and the title compound was obtained (5.8 g, 0.014 mmol, 96%) as a yellow oil.

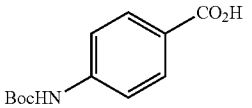
[0463] ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.21 (s, 1H$_{_OH}$), 8.81 (s, 1H$_{_NH}$), 8.49 (d, J=8.5 Hz, 1H), 7.69 (dd, J=8.5, 1.8 Hz, 1H), 7.58 (d, J=1.7 Hz, 1H), 7.07 (d, J=8.8 Hz, 1H), 6.28 (d, J=8.7 Hz, 1H), 4.80-4.72 (m, 1H), 4.72-4.63 (m, 1H), 4.28 (s, 2H$_{_NH2}$), 3.91 (s, 3H), 1.44 (d, J=6.1 Hz, 6H), 1.34 (d, J=6.2 Hz, 7H) ppm.

[0464] ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 166.9, 156.4, 146.5, 146.0, 132.7, 132.0, 125.1, 123.40, 121.5, 119.1, 113.4, 106.5, 106.3, 77.4, 74.4, 72.0, 52.3, 22.9, 22.4 ppm.

[0465] HRMS (ESI): Calculated for $C_{21}H_{25}N_2O_6$ $(M-H)^-$: 401.1713. found: 401.1716.

4-(tert-butoxycarbonylamino)benzoic acid

[0466]



[0467] 4-Aminobenzoic acid (1.00 g, 7.29 mmol) was dissolved in 1,4-dioxane (15 mL) and H_2O (7 mL). Et_3N (2.0 mL, 14.58 mmol) was added to the solution and the reaction mixture was stirred for 5 minutes at room temperature. Di-tert-butyl dicarbonate (3.18 g, 14.58 m mol) was then added to the solution in one portion and the reaction mixture was stirred for 24 hours. Following removal of the solvent in vacuo, 3M HCl was added to the residue yielding a white precipitate. The slurry was then filtered and washed with H_2O before drying in under high vacuum. Recrystallization from hot methanol yielded the titled compound as a colorless solid (1.63 g, 6.85 mmol, 94% yield).

[0468] mp: 192-194° C.

[0469] ^{1}H NMR (400 MHz, DMSO) δ 9.73 (s, 1H$_{_CO2H}$), 7.83 (d, 2H, J=8.9 Hz), 7.55 (d, 2H, J=8.9 Hz), 1.47 (s, 9H) ppm.

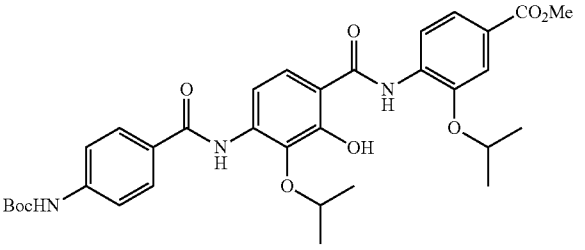
[0470] ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 152.6, 143.8, 130.4, 124.0, 117.2, 79.7, 28.1 ppm.

[0471] HRMS (ESI): Calculated for $C_{12}H_{15}NnaO_4$ $(M+Na)^+$: 260.0893. found: 260.0897.

[0472] The spectroscopic data are in accordance with those reported in the literature (*J. Am. Chem. Soc.* 2012, 134, 7406-7413).

Methyl-4-(4-(4-(tert-butoxycarbonyl)amino)benzamido)-2-hydroxy-3-isopropxybenzamido)-3-isopropoxybenzoate

[0473]



[0474] 4-(Tert-butoxycarbonylamino)benzoic acid (40.0 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (8.4 mL) and pre-activated with Ghosez's reagent (22.5 μL, 0.17 mmol) for 2 hours at room temperature. 4-(4-Amino-2-hydroxy-3-isopropoxybenzamido)-3-isopropoxybenzoate (68.4 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (8.4 mL) and N,N-diisopropylethylamine (DIPEA) was added (59.2 μL, 0.34 mmol). The solution containing the acid chloride was then added and the reaction mixture stirred for 1 day at room temperaturet. The solvent was then removed and the crude product was purified by preparative HPLC (RP-18; run time 100 min; H_2O/MeCN=100:0→0:100; tr=70 min) providing the title compound as a light yellow oil (47.3 mg, 0.076 mmol, 72%).

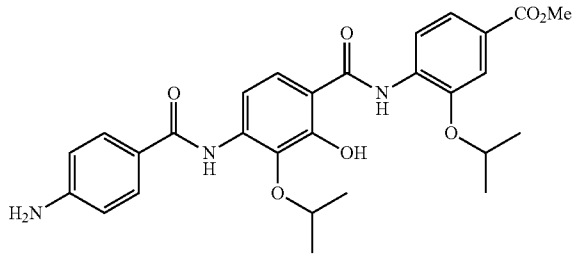
[0475] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J=7.5 Hz, 2H), 7.78 (d, J=1.4 Hz, 1H), 7.72 (dd, J=7.5, 1.4 Hz, 1H), 7.69 (s, 1H$_{_NH}$), 7.68 (d, J=7.3 Hz, 3H), 7.56 (d, J=7.5 Hz, 1H), 7.17 (d, J=7.5 Hz, 1H), 5.72 (s, 1H$_{_NH}$), 5.49 (s, 1H$_{_NH}$), 4.02-3.96 (m, 2H), 3.95 (d, J=3.7 Hz, 3H), 1.49 (s, 9H), 1.46 (d, J=5.6 Hz, 6H), 1.41 (d, J=5.5 Hz, 6H) ppm.

[0476] ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.89, 166.67, 166.61, 158.88, 154.93, 146.90, 141.47, 135.07, 134.68, 131.70, 130.38, 130.38, 127.26, 127.17, 123.25, 121.40, 120.63, 120.63, 115.87, 114.85, 113.39, 106.06, 80.65, 75.89, 74.13, 52.08, 28.41, 28.41, 28.41, 21.80, 21.80, 21.80, 21.80 ppm.

[0477] HRMS (ESI): Calculated for $C_{33}H_{38}N_3O_9$ $(M-H)^-$: 620.2687. found: 620.2689.

Methyl-4-(4-(4-aminobenzamido)-2-hydroxy-3-isopropxybenzamido)-3-isopropoxybenzoate

[0478]



[0479] Methyl-4-(4-(4-(tert-butoxycarbonyl)amino)benzamido)-2-hydroxy-3-isopropxybenzamido)-3-isopropoxybenzoate (40.0 mg, 0.064 mmol) was dissolved in a mixture 10/1 dichloromethane/trifluoroacetic acid (1 mL) and stirred 17 hours at room temperature. The solvent was removed under reduced pressure and the residual acid was removed under high vacuum to give the titled compound (33.4 mg, 0.064 mmol, quantitative) as yellow oil.

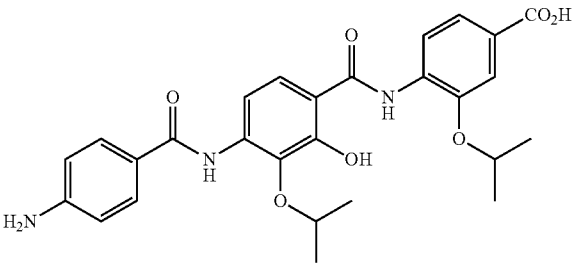
[0480] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J=1.4 Hz, 1H), 7.83 (s, 1H$_{_NH}$), 7.79 (dd, J=7.5, 1.4 Hz, 1H), 7.75 (d, J=7.5 Hz, 1H), 7.70 (d, J=7.5 Hz, 2H), 7.65 (d, J=7.5 Hz, 1H), 7.05 (d, J=7.5 Hz, 1H), 6.94 (s, 1H$_{_NH}$), 6.75 (d, J=7.5 Hz, 2H), 6.09 (s, 1H$_{_OH}$), 4.02-3.97 (m, 1H), 3.95-3.89 (s, 3H), 3.92 (m, 1H), 3.85 (s, 2H$_{_NH}$), 1.47 (d, J=5.7 Hz, 6H), 1.40 (d, J=5.5 Hz, 6H) ppm.

[0481] ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.89, 166.67, 166.61, 158.88, 152.59, 146.90, 135.07, 134.68, 131.70, 130.93, 130.93, 127.17, 123.25, 122.42, 121.40, 115.87, 114.85, 114.35, 114.35, 113.39, 106.06, 75.89, 74.13, 52.08, 21.80, 21.80, 21.80, 21.80 ppm.

[0482] HRMS (ESI): Calculated for $C_{28}H_{32}N_3O_7(M+H)^+$: 522.2162. found: 522.2160.

Cystobactamide C

[0483]



[0484] Methyl-4-[4-(4-aminobenzamido)-2-hyd roxy-3-isopropxybenzamido]-3-isopropoxybenzoate (30.0 mg, 0.058 mmol) was dissolved in a mixture 1/1 of THF/H_2O (0.3/0.3 mL). Then, solid LiOH (13.9 mg, 0.58 mmol) was added and the reaction mixture was stirred at room temperature for 17 hours. The aqueous layer was acidified with 1M HCl until pH-1 and extracted with ethyl acetate (3×). The organic extracts were combined, dried over anhydrous $MgSO_4$ and filtered. The solvent was concentrated in vacuo to yield the title compound (27.4 mg, 0.054 mmol, 93%) as a yellow oil.

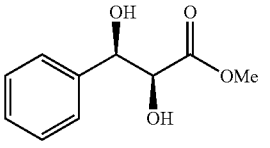
[0485] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J=1.4 Hz, 1H), 7.87 (dd, J=7.5, 1.4 Hz, 1H), 7.70 (d, J=7.5 Hz, 2H), 7.65 (d, J=7.5 Hz, 1H), 7.53 (d, J=7.5 Hz, 1H), 7.05 (d, J=7.5 Hz, 1H), 6.95 (s, 1H$_{_NH}$), 6.77 (s, 1H$_{_NH}$), 6.75 (d, J=7.5 Hz, 2H), 6.12 (s, 1H$_{_OH}$), 3.97-3.89 (m, 2H), 3.85 (s, 2H$_{_NH}$), 1.40 (d, J=5.5 Hz, 6H), 1.39 (d, J=5.5 Hz, 6H) ppm.

[0486] ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.79, 166.67, 166.61, 158.88, 152.59, 149.81, 136.38, 135.07, 134.68, 130.93, 130.93, 125.08, 123.25, 122.80, 122.42, 120.37, 114.35, 114.35, 113.76, 113.39, 106.06, 75.89, 74.13, 21.80, 21.80, 21.80, 21.80 ppm.

[0487] HRMS (ESI): Calculated for $C_{28}H_{32}N_3O_7$ $(M+H)^+$: 508.2006. found: 508.2008.

(2S,3R)-Methyl 2,3-dihydroxy-3-phenylpropanoate

[0488]



[0489] AD mix β (20.0 g) was dissolved in a mixture of tBuOH/H_2O (1:1; 142 mL) at 25° C. Afterwards, $CH_3SO_2NH_2$ (1.36 g, 14.3 mmol, 1.0 eq.) was added and the reaction mixture cooled to 0° C. Then, methylcinnamate (2.31 g, 14.3 mmol, 1.0 eq.) was added and the resulting mixture was vigorously stirred for 16 h at 0° C. Stirring was continued for additional 6 h at 25° C. The reaction mixture was hydrolyzed by addition of an aqueous Na_2SO_3 solution (21.4 g, 170 mmol, 12.0 eq.) and stirring was continued for additional 2.5 h. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with EtOAc (3×). The combined organic layers

were washed with H_2O (1×) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate=1:1) afforded the desired diol (2.21 g, 11.3 mmol, 79%) as a colorless solid. The spectroscopic data are in accordance with those reported in the literature.

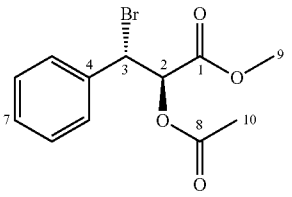
[0490] R_f=0.38 (PE/EtOAc 1:1); m.p.=84-85° C. (lit: m.p. =80-81° C.); $[\alpha]_D^{20}$=−9.8° (c 1.28, $CHCl_3$) {lit.: $[\alpha]_D^{26}$=−9. 8° (c 1.07, $CHCl_3$)};

[0491] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=7.42-7.29 (5H, m, ArH), 5.03 (1H, dd, J=2.7, 7.2 Hz, H-3), 4.38 (1H, dd, J=2.7, 6.0 Hz, H-2), 3.82 (3H, s, H-8), 3.12 (1H, d, J=6.0 Hz, OH-□), 2.76 (1H, d, J=7.2 Hz, OH-β) ppm;

[0492] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.16 ppm): δ=173.3 (q, C-1), 140.1 (q, C-4), 128.6 (2C, t, C-6), 128.3 (t, C-7), 126.3 (2C, t, C-5), 74.8 (t, C-2), 74.6 (t, C-3), 53.1 (p, C-8) ppm; HRMS (ESI): m/z calculated for $C_{10}H_{12}O_4Na$ $[M+Na]^+$: 219.0633. found 219.0633.

(2R,3S)-Methyl
2-acetoxy-3-bromo-3-phenylpropanoate (3)

[0493]



[0494] To (2S,3R)-Methyl 2,3-dihydroxy-3-phenylpropanoate (2.15 g, 10.9 mmol, 1.0 eq.) was added HBr/HOAc (33%; 16.9 mL) dropwise at 25° C. The resulting mixture was heated to 45° C. and stirred for 30 min. Then, the reaction mixture was cooled to 25° C. and poured into an ice-cooled $NaHCO_3$-solution (40 mL). The aqueous layer was extracted with Et_2O (3×). The combined organic layers were washed with H_2O (1×) and with brine. Then, the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate=12.5:1) gave the title compound (2.32 g, 7.71 mmol, 71%) as a colorless solid. The spectroscopic data are in accordance with those reported in the literature.

[0495] R_f=0.79 (PE/EtOAc 1:1); m.p.=78-82° C. (lit: m.p. =78-79° C.); $[\alpha]_D^{20}$=+89.9° (c 1.74, $CHCl_3$) {Lit.: $[\alpha]_D^{26}$=+ 100.3° (c 1.36, $CHCl_3$)};

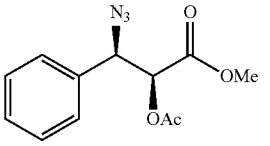
[0496] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=7.46-7.44 (2H, m, H-6), 7.36-7.30 (3H, m, H-5, H-7), 5.65 (1H, d, J=6.3 Hz, H-3), 5.35 (1H, d, J=6.3 Hz, H-2), 3.71 (3H, s, H-9), 2.11 (3H, s, H-10) ppm;

[0497] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.16 ppm): δ=169.7 (q, C-1), 167.5 (q, C-8), 136.8 (q, C-4), 129.3 (t, C-7), 128.7 (4C, t, C-5, C-6), 75.4 (t, C-3), 52.9 (p, C-9), 49.3 (t, C-2), 20.6 (p, C-10) ppm;

[0498] HRMS (ESI): m/z calculated for $C_{12}H_{13}O_4BrNa$ [M+Na]: 322.9895. found 322.9891.

(2S,3R)-Methyl
2-acetoxy-3-azido-3-phenylpropanoate

[0499]



[0500] (2S,3R)-Methyl 2-acetoxy-3-azido-3-phenylpropanoate (2.27 g, 7.55 mmol, 1.0 eq.) was dissolved in DMF (27.0 mL) at 25° C. Then, NaN_3 (1.96 g, 30.2 mmol, 4.0 eq.) was added and the resulting mixture was heated up to 40° C. for 3 h. After cooling the reaction mixture was cooled to 25° C. and EtOAc was added. The organic layer was washed with H_2O (2×), followed by brine (1×). The combined, organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate=10:1) afforded the title compound (1.77 g, 6.71 mmol, 89%) as yellow oil. The spectroscopic data are in accordance with those reported in the literature.

[0501] R_f=0.24 (PE/EtOAc=10:1); $[\alpha]_D^{20}$=−97.8° (c 2.3, $CHCl_3$); {lit.: $[\alpha]_D^{26}$=−104.2° (c 2.33, $CHCl_3$)};

[0502] IR: $\tilde{\nu}$=2955 (w), 2103 (s, azide), 1747 (s, C═O), 1495 (w), 1454 (m), 1437 (m), 1373 (m), 1210 (s), 1099 (m), 1030 (m), 910 (m), 751 (m), 701 (s) cm^{-1};

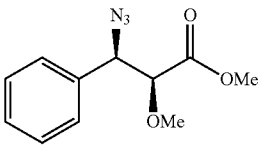
[0503] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=7.42-7.33 (5H, m, ArH), 5.24 (1H, d, J=4.8 Hz, H-2), 5.07 (1H, d, J=4.8 Hz, H-3), 3.69 (3H, s, H-9), 2.14 (3H, s, H-10) ppm;

[0504] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.16 ppm): δ=169.9 (q, C-1), 168.0 (q, C-8), 134.6 (q, C-4), 129.3 (t, C-7), 129.0 (2C, t, C-6), 127.6 (2C, t, C-5), 74.9 (t, C-2), 65.4 (t, C-3), 52.8 (p, C-9), 20.5 (p, C-10) ppm;

[0505] HRMS (ESI): m/z calculated for $C_{12}H_{13}N_3O_4Na$ $[M+Na]^+$: 286.0804. found 286.0805.

(2S,3R)-Methyl
3-azido-2-methoxy-3-phenylpropanoate

[0506]



[0507] (2S,3R)-Methyl 2-acetoxy-3-azido-3-phenylpropanoate (2.5 g, 1.0 eq) was dissolved in 190 ml THF at 0° C. Then a solution of KOH (0.5M, 10.0 eq) was added dropwise and the reaction mixture was stirred at 0° C. for 5 h. Afterwards, aqueous 2N HCl was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate. The organic phases were combined and dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the

crude acid which was directly used for the next step without further purification. The crude material (0.5 g, 1.0 eq) was dissolved in 17 ml methyl iodide. Then, $CaSO_4$ (2.6 g, 8.0 eq) and Ag_2O (1.7 g, 3.0 eq) were added and stirring of the suspension was carried out in the dark at room temperature for 22 h. Then, the crude mixture was filtered and concentrated in vacuum to give the title compound (70% yield) which can be directly used in the next step without further purification.

[0508] $[\alpha]_D^{20}=-143.7°$ (c 1.1, $CHCl_3$);

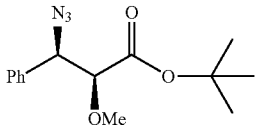
[0509] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=3.44 (s, 3H), 3.61 (s, 3H), 3.94 (d, J=6.4 Hz, 1H), 4.79 (d, J=6.4 Hz, 1H), 7.35-7.36 (m, 5H);

[0510] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.0 ppm): δ=52.2, 59.1, 66.9, 84.7, 127.7, 128.7, 128.9, 135.1, 170.0;

[0511] HRMS (ESI): m/z calculated for $C_{11}H_{13}N_3O_3Na$ $[M+Na]^+$: 258.0855. found 258.0852.

(2S,3S)-tert-Butyl
3-azido-2-methoxy-3-phenylpropanoate

[0512]



[0513] To a stirred solution of (2S,3R)-Methyl 3-azido-2-methoxy-3-phenylpropanoate (1.2 g, 1.0 eq) in 100 ml THF was added an aqueous solution of KOH (0.5 M, 10.0 eq) dropwise. The reaction mixture was stirred for 5 h at rt and hydrolyzed by addition of 2N HCl. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give carboxylic acid (1.2 g, 98% yield) which was subjected to the next reaction without further purification. Crude acid (0.3 g, 1.0 eq) and 3.9 ml dimethylformamide di-tert-butyl acetal (3.9 ml, 12 eq) were dissolved in 8 ml toluene at room temperature. The resulting reaction mixture was heated up to 80° C. and stirred for 7 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate=30:1) to afford the title compound (0.34 g, 89% yield).

[0514] $[\alpha]_D^{20}=-113.3°$ (c 1.0, $CHCl_3$);

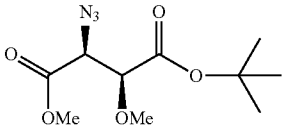
[0515] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=1.26 (s, 9H), 3.45 (s, 3H), 3.85 (d, J=7.2 Hz, 1H), 4.70 (d, J=7.2 Hz, 1H), 7.34-7.35 (m, 5H);

[0516] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.0 ppm): δ=27.7, 58.6, 67.2, 82.3, 85.1, 128.2, 128.6, 128.9, 135.2, 168.5;

[0517] HRMS (ESI): m/z calculated for $C_{14}H_{19}O_3N_3Na$ $[M+Na]^+$: 300.1324. found 300.1332.

(2S,3S)-4-tert-Butyl 1-methyl
2-azido-3-methoxysuccinate

[0518]



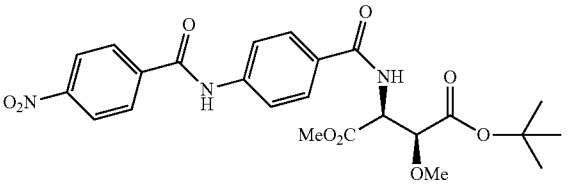
[0519] To a stirred solution of (2S,3S)-tert-butyl 3-azido-2-methoxy-3-phenylpropanoate (310 mg, 1.0 eq) in a solvent mixture of 3 ml $CHCl_3$, 13 ml CH_3CN and 26 ml H_2O $NaIO_4$ (7.2 g, 30 eq) and $RuCl_3$ (0.3 eq, 69 mg) were added portionwise at room temperature. The reaction mixture was heated under refluxing conditions for 3 h. A white precipitate formed upon cooling to room temperature. The solid was filtered off and the filtrate was extracted with diethyl ether. The combined organic phases were concentrated under reduced pressure to yield the crude product. This material was dissolved in 9 ml methyl iodide. Then, $CaSO_4$ (1.2 g, 8.0 eq) and Ag_2O (778 mg, 3.0 eq) were added and the reaction mixture was stirred in the dark at room temperature for 22 h. After filtration the filtrate was concentrated under reduced pressure to afford the title compound in pure form so that it can directly be employed in the next step without further purification.

[0520] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=1.51 (s, 3H), 3.48 (s, 3H), 4.15 (d, J=3.6 Hz, 1H), 4.21 (d, J=4.0 Hz, 1H);

[0521] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.0 ppm): δ=28.1, 53.0, 59.5, 63.4, 81.2, 83.0, 167.7, 168.3.

(2S,3R)-1-tert-Butyl 4-methyl 2-methoxy-3-[4-(4-nitrobenzamido)benzamido]succinate

[0522]



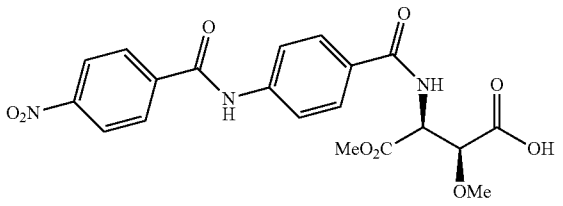
[0523] The crude mixture (2S,3S)-4-tert-butyl 1-methyl 2-azido-3-methoxysuccinate was dissolved in 12 ml THF, then 0.5 ml water and PPh_3 (881 mg, 3.0 eq) were added. The resulting reaction mixture was warmed up to 50° C. and stirring was continued for 12 hours. Then, the solvent was removed under reduced pressure to afford the crude product which was pure enough to be used directly in the next step. The crude product was dissolved in 5 ml DMF and (ethyl carbonic) 4-(4-nitrobenzamido)benzoic anhydride (481 mg, 1.2 eq) was added at room temperature. After stirring for 20 h, water was added and the aqueous solution was extracted with ethyl acetate. The combined organic phases were concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate=2:1) afforded the title compound (81 mg, 16% over four steps).

[0524] $[\alpha]_D^{20}$=−11.8° (c 1.1, $CHCl_3$);

[0525] ^{1}H-NMR (400 MHz, $CDCl_3$, $CHCl_3$=7.26 ppm): δ=1.41 (s, 9H), 3.45 (s, 3H), 3.78 (s, 3H), 4.34 (d, J=2.4 Hz, 1H), 5.29 (dd, J=2.4, 9.6 Hz, 1H), 6.76 (d, J=9.6 Hz, 1H), 7.27-7.35 (m, 4H), 8.07 (d, J=8.8 Hz, 2H), 8.26 (2, J=8.8 Hz, 2H), 8.83 (s, 1H);

[0526] ^{13}C-NMR (100 MHz, $CDCl_3$, $CHCl_3$=77.0 ppm): δ=27.9, 52.9, 54.8, 59.1, 79.8, 83.2, 120.1, 123.8, 128.3, 128.7, 129.6, 140.3, 141.1, 149.7, 164.1, 166.9, 168.0, 169.7.

[0527] HRMS (ESI): m/z calculated for $C_{24}H_{27}O_9N_3Na$ $[M+Na]^+$: 524.1645. found 524.1647.



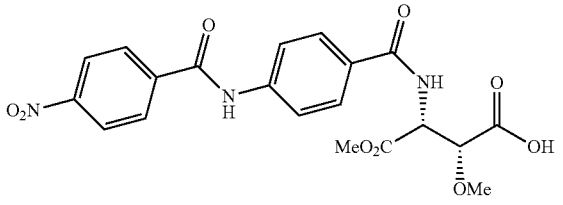
[0528] To a stirred solution of (2S,3R)-1-tert-Butyl 4-methyl 2-methoxy-3-[4-(4-nitrobenzamido)benzamido]succinate (74.3 mg, 0.15 mmol) in 2.5 ml CH_2Cl_2 was added 1.5 ml TFA at room temperature. After stirring for 5 h, the reaction mixture was added water and extracted with ethyl acetate. The combined organic phases were washed with water (three times), dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound in quantitative yield (65.9 mg, quant.).

[0529] $[\alpha]_D^{20}$=−16.4° (c 1.1, EtOAc);

[0530] ^{1}H-NMR (400 MHz, DMSO, DMSO=2.50 ppm): δ=3.37 (s, 3H), 3.69 (s, J=3H), 4.34 (d, J=4.4 Hz, 1H), 5.09 (dd, J=4.8, 8.8 Hz, 1H), 7.89-7.90 (m, 4H), 8.21 (dd, J=2, 6.8 Hz, 1H), 8.39 (dd, J=2, 6.8 Hz, 1H), 8.55 (d, J=8.8 Hz, 1H), 10.8 (s, 1H).

[0531] ^{13}C-NMR (100 MHz, DMSO, DMSO=40.0 ppm): δ=52.9, 54.8, 58.7, 79.5, 120.0, 124.1, 129.0, 129.2, 129.8, 140.8, 142.2, 149.8, 164.7, 166.6, 170.2, 170.9. HRMS (ESI): m/z calculated for $C_{20}H_{19}O_9N_3Na$ $[M+Na]^+$: 468.1019. found 468.1016.

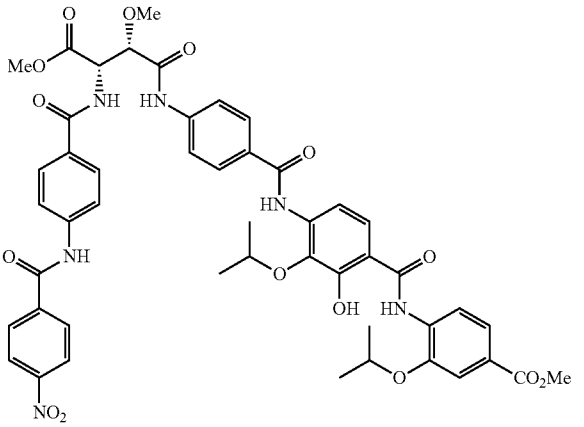
[0532] Optical rotation of other enantiomer:



(ent)-D

[0533] $[\alpha]_D^{20}$=+13.9° (c 1.1, EtOAc);

[0534] Methyl-4-(4-(4-((2S,3S)-2,4-dimethoxy-3-(4-(4-nitrobenzamido)benzamido)-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropxybenzamido)-3-isopropoxybenzoate



[0535] Methyl-4-[4-(4-aminobenzamido)-2-hydroxy-3-isopropoxybenzamido]-3-isopropoxybenzoate (15.3 mg, 0.029 mmol) and (2S,3R)-2,4-dimethoxy-3-[4-(4-nitrobenzamido)benzamido]succinate (14.2 mg, 0.032 mmol) were dissolved in CH_2Cl_2 (3.4 mL) and cooled to 0° C. Then, HOAt (5.9 mg, 0.044 mmol), DIPEA (7.7 μL, 0.044 mmol), and EDC.HCl (6.9 mg, 0.036 mmol) were added. The mixture was stirred from 0° C. to room temperature for 17 hours. The solvent was concentrated in vacuo to give an oily residue, which was purified by flash chromatography (petroleum ether/ethyl acetate=94/6) to yield the title compound (20.1 mg, 0.021 mmol, 73%) as a colourless oil.

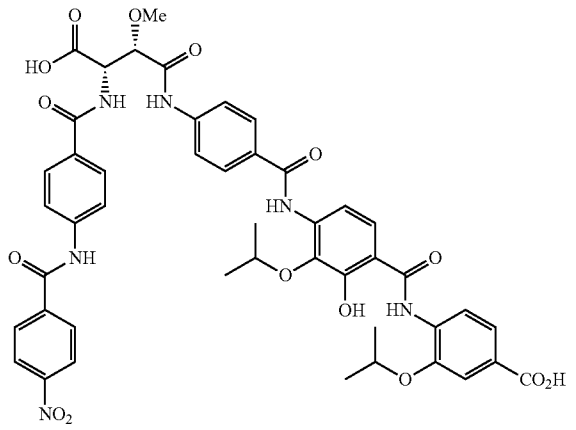
[0536] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H$_{_OH}$), 8.37 (d, J=7.5 Hz, 2H), 8.20 (d, J=7.5 Hz, 2H), 8.11 (s, 1H$_{_NH}$), 8.02 (s, 1H$_{_NH}$), 8.01 (d, J=1.4 Hz, 2H), 7.98 (d, J=7.5 Hz, 2H), 7.90 (d, J=1.3 Hz, 1H), 7.81 (dd, J=7.5, 1.4 Hz, 1H), 7.78 (d, J=7.4 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H), 7.61 (d, J=7.5 Hz, 2H), 7.55 (s, 1H), 7.54 (s, 1H$_{_NH}$), 7.53 (s, 1H), 7.41 (d, J=7.5 Hz, 1H), 5.72 (s, 1H$_{_NH}$), 5.63 (s, 1H$_{_NH}$), 5.10 (d, J=3.8 Hz, 1H), 4.76 (d, J=3.8 Hz, 1H), 4.04-3.98 (m, 2H), 3.97 (s, J=3.1 Hz, 3H), 3.74 (s, 3H), 3.32 (s, 3H), 1.47 (d, J=5.7 Hz, 6H), 1.39 (d, J=5.7 Hz, 6H) ppm.

[0537] ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.30, 168.15, 168.07, 167.77, 166.93, 166.88, 166.82, 158.83, 151.01, 146.97, 140.78, 139.42, 138.71, 134.97, 134.55, 131.57, 130.00, 130.00, 129.41, 129.41, 129.39, 129.39, 128.12, 127.53, 127.24, 124.17, 124.17, 123.28, 122.61, 122.61, 121.78, 121.78, 121.44, 115.94, 114.88, 113.30, 106.09, 78.00, 75.89, 74.13, 58.51, 56.50, 52.17, 52.08, 21.80, 21.80, 21.80, 21.80 ppm.

[0538] HRMS (ESI): Calculated for $C_{48}H_{47}N_6O_{15}$ $(M-H)^-$: 947.3178. found: 947.3175.

Cystobactamide A

[0539]



[0540] Methyl-4-4-[4-((2S,3S)-2,4-dimethoxy-3-(4-(4-nitrobenzamido)benzamido)-4-oxobutanamido]benzamido)-2-hydroxy-3-isopropxybenzamido)-3-isopropoxybenzoate (15.2 mg, 0.016 mmol) was dissolved in a mixture 1/1 of THF/H_2O (0.2/0.2 mL). Then, solid LiOH (3.8 mg, 0.16 mmol) was added and the reaction mixture was stirred at room temperature for 17 hours. The aqueous layer was acidified with 1M HCl until pH-1 and extracted with ethyl acetate (3×). The organic extracts were combined, dried over $MgSO_4$ and filtered. The solvent was concentrated in vacuo to yield the title compound (13.3 mg, 0.014 mmol, 90%) as a yellow wax.

[0541] $[\alpha]_D^{20}=-19.1°$ (c 1.1, EtOAc)

[0542] ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J=7.5 Hz, 2H), 8.15 (d, J=7.5 Hz, 2H), 8.00 (d, J=1.8 Hz, 2H), 7.98 (d, J=1.8 Hz, 2H), 7.90 (d, J=1.8 Hz, 1H), 7.86 (dd, J=7.5, 1.8 Hz, 1H), 7.78 (d, J=7.5 Hz, 1H), 7.65 (s, 1H), 7.63 (d, J=7.5 Hz, 2H), 7.58 (s, 1H$_{-N}$H), 7.54 (d, J=7.5 Hz, 2H), 7.51 (s, 1H$_{-NH}$), 7.10 (s, 1H$_{-NH}$), 7.03 (d, J=7.5 Hz, 1H), 6.35 (s, 1H$_{-NH}$), 5.57 (s, 1H$_{-NH}$), 5.42 (s, 1H$_{-OH}$), 4.93 (s, 1H), 4.70 (s, 1H), 4.01 (hept, J=5.6 Hz, 1H), 3.95 (hept, J=5.6 Hz, 1H), 3.38 (s, 3H), 1.48 (s, 6H), 1.47 (s, 6H) ppm.

[0543] ^{13}C NMR (100 MHz $CDCl_3$) δ 173.30, 169.54, 168.18, 168.07, 167.77, 166.88, 166.82, 158.83, 151.01, 149.88, 140.78, 139.42, 138.71, 136.26, 134.97, 134.55, 130.00, 130.00, 129.41, 129.41, 129.39, 129.39, 128.12, 127.53, 125.15, 124.17, 124.17, 123.28, 122.84, 122.61, 122.61, 121.78, 121.78, 120.41, 113.82, 113.30, 106.09, 77.86, 75.89, 74.13, 58.51, 54.58, 21.80, 21.80, 21.80, 21.80 ppm.

[0544] HRMS (ESI): Calculated for $C_{46}H_{43}N_6O_{15}$ $(M-H)^-$: 920.2865. found: 920.2866.

Synthesis of Cystobactamide C Derivatives

[0545]

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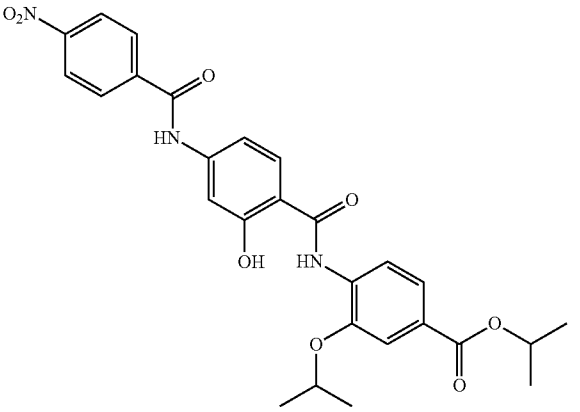

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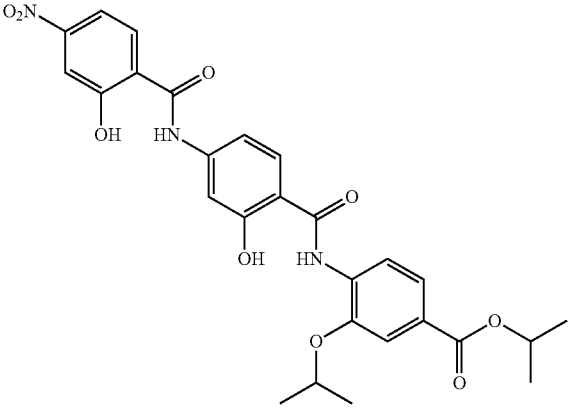

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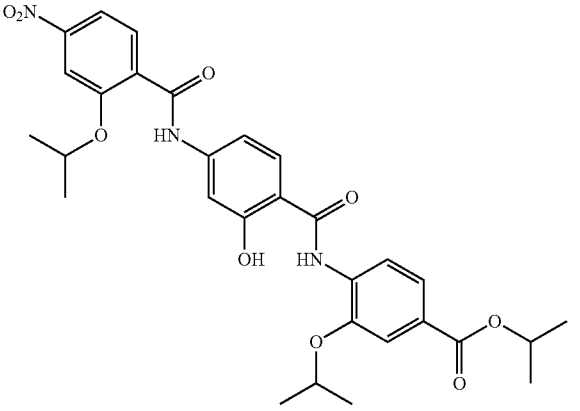

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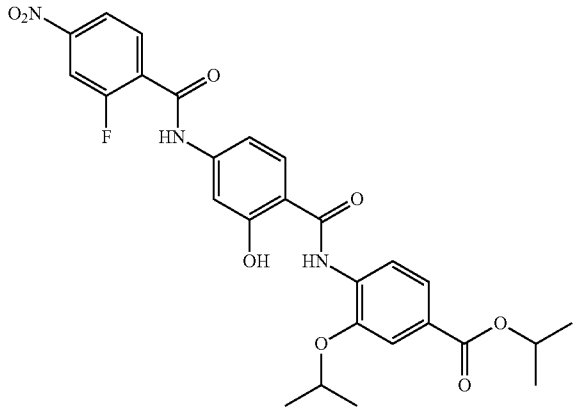

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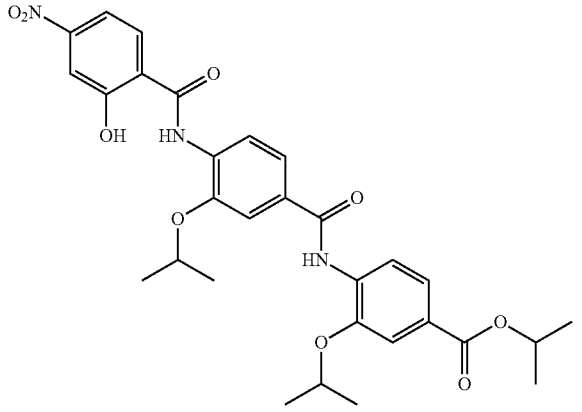

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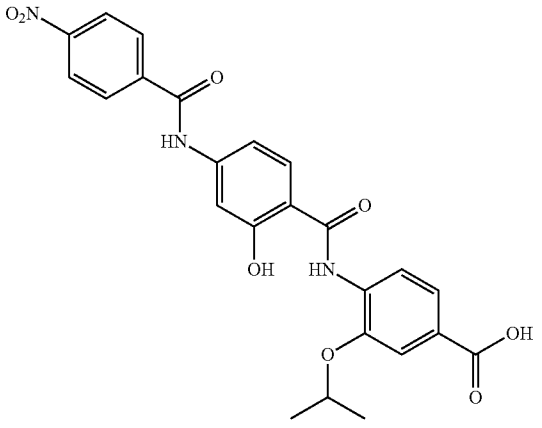

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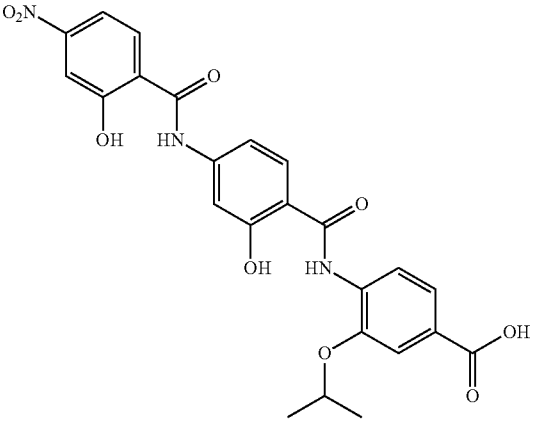
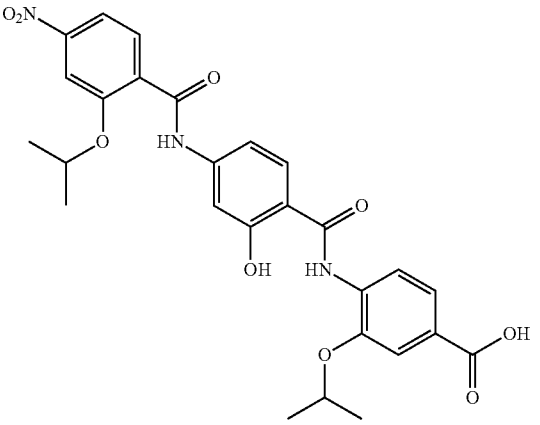
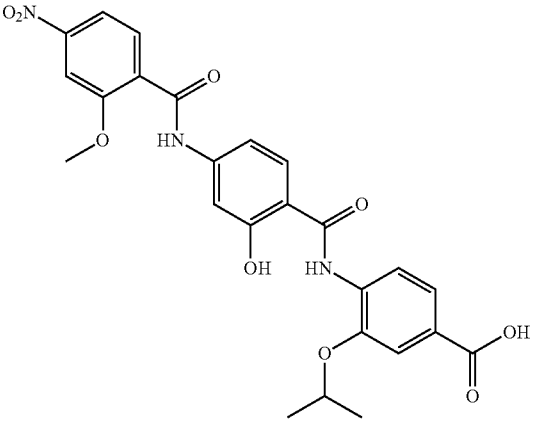
(7a)



(8a)



(9a)



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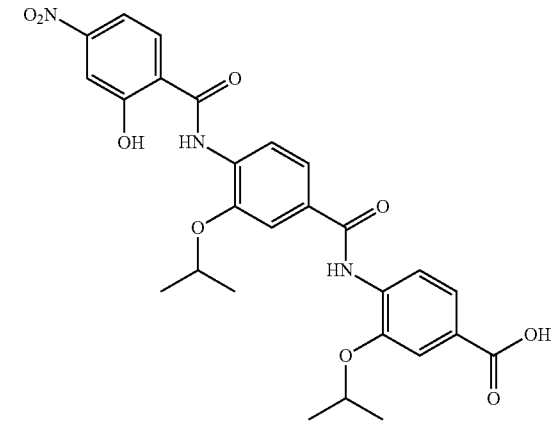
(10a)



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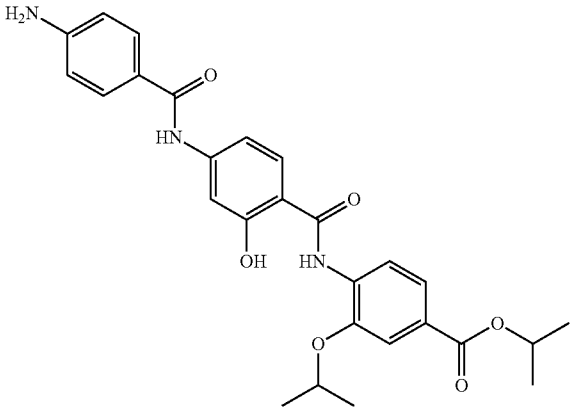

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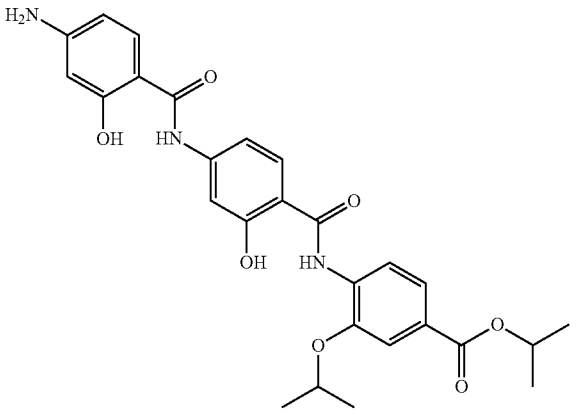

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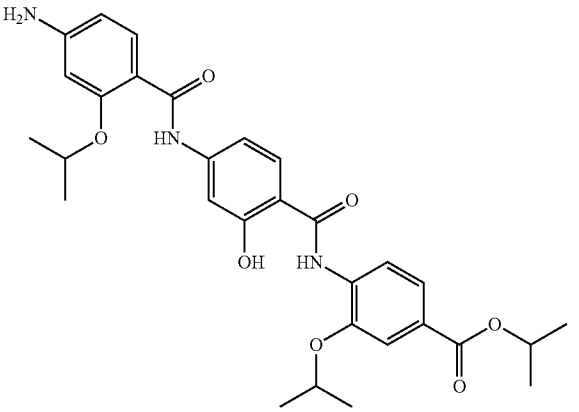

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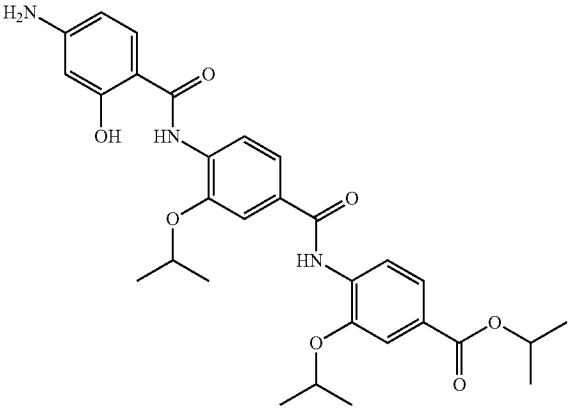

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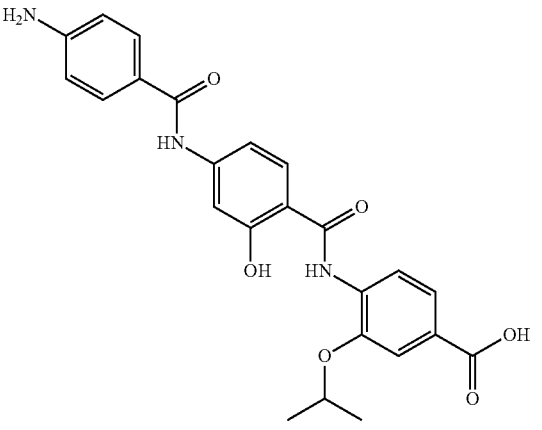

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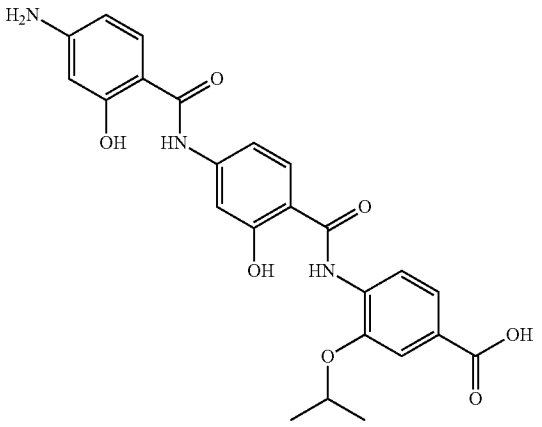

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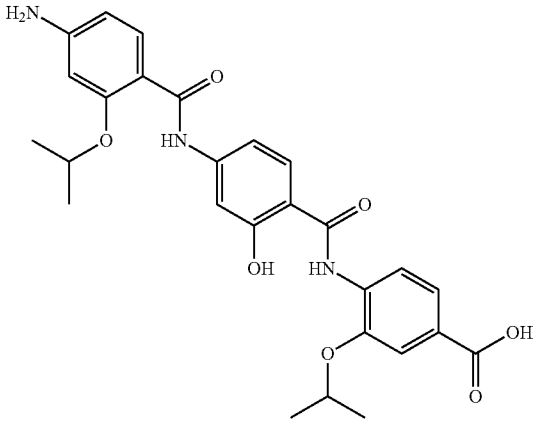

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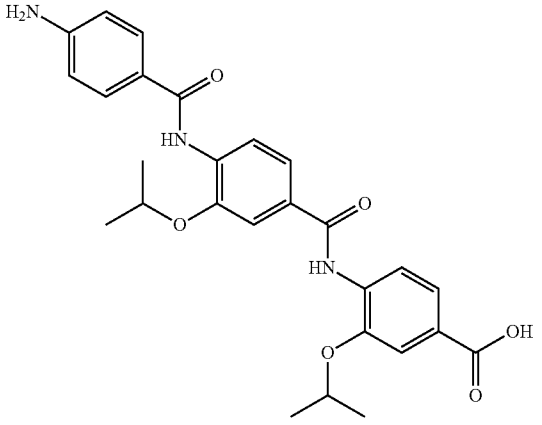

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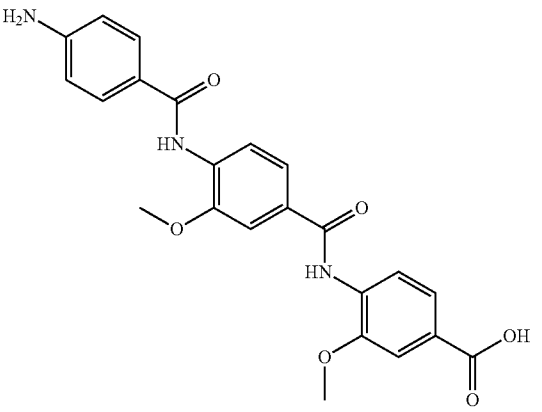

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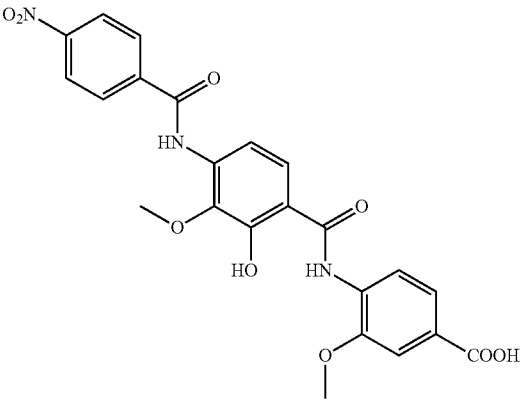

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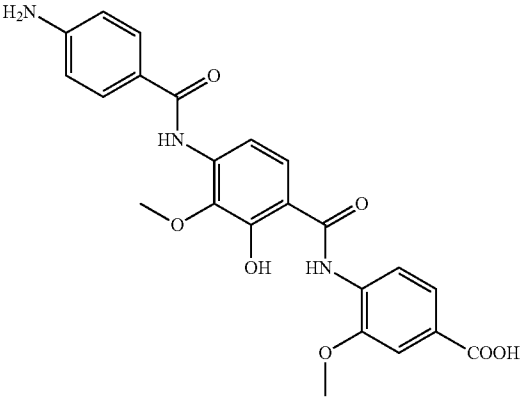

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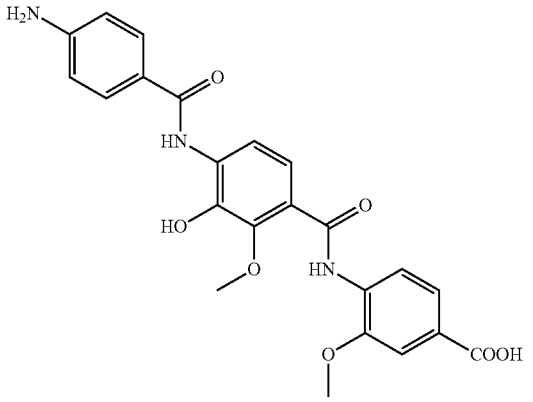

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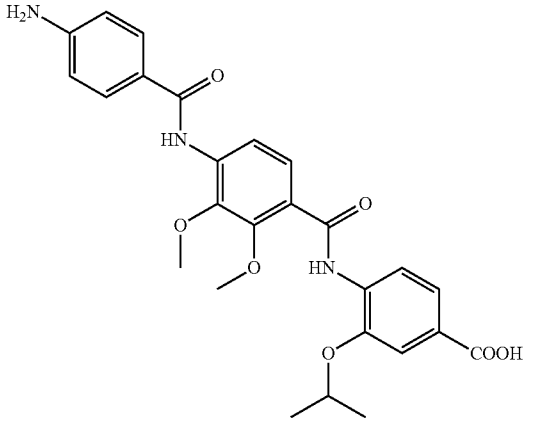

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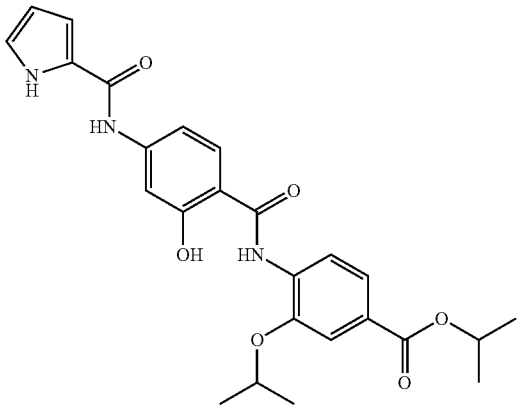

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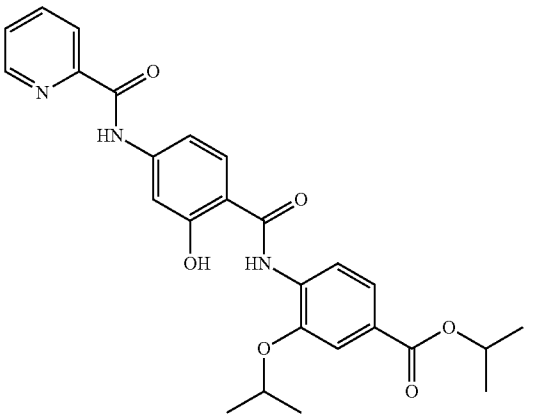

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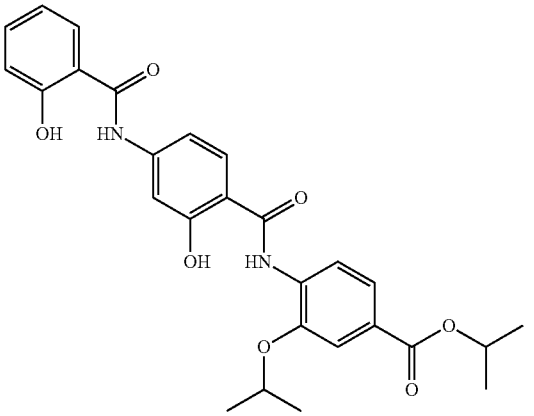

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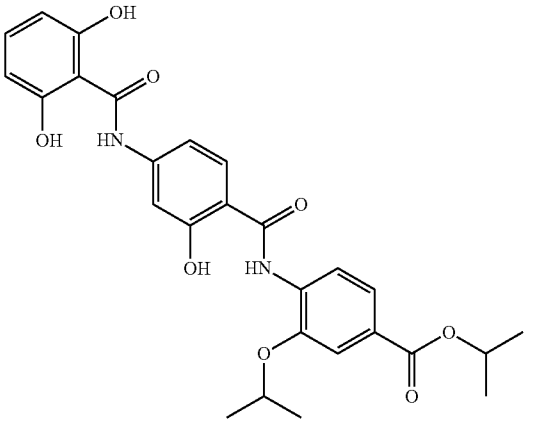

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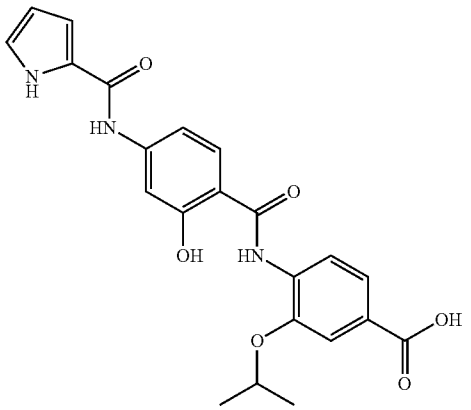

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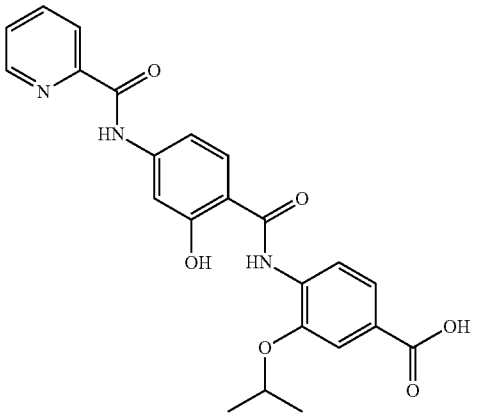

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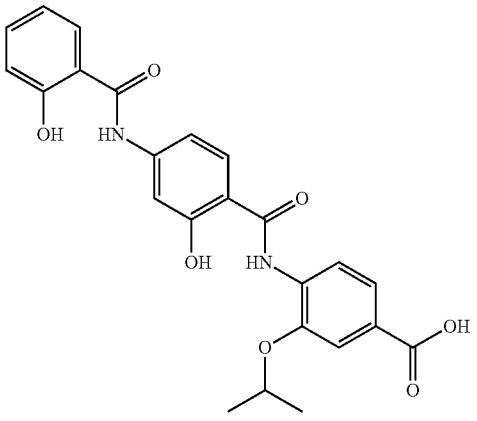

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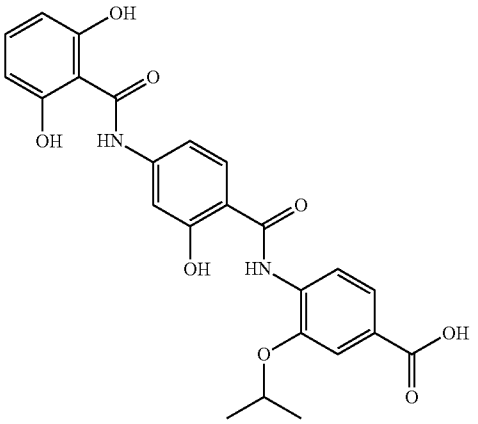

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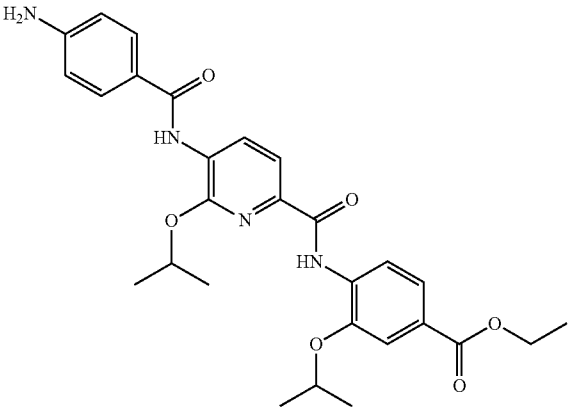

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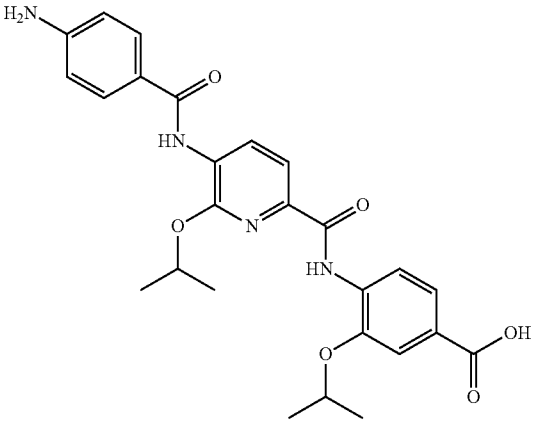
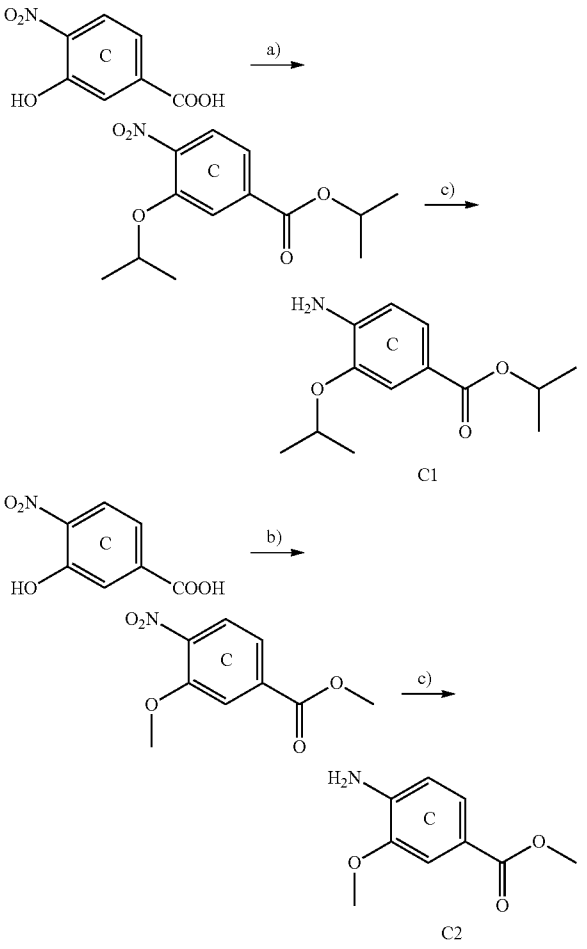


1.1. Synthesis of the Different Used Individual Rings

[0546] The preparation of the different individual rings that were used during the synthesis of the cystobactamide C derivatives is described here.

Preparation of Ring C

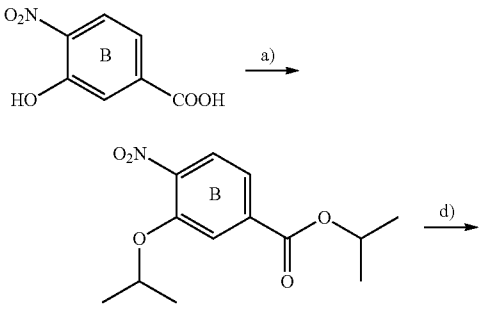
[0547]



a) $BrCH(CH_3)_2$, K_2CO_3, DMF, 90° C., overnight; b) $SO_2(OMe)_2$, K_2CO_3, DMF, 90° C., overnight; c) Fe, NH_4Cl, $EtOH/H_2O$, reflux, 2 hours

Preparation of Ring B

[0548]



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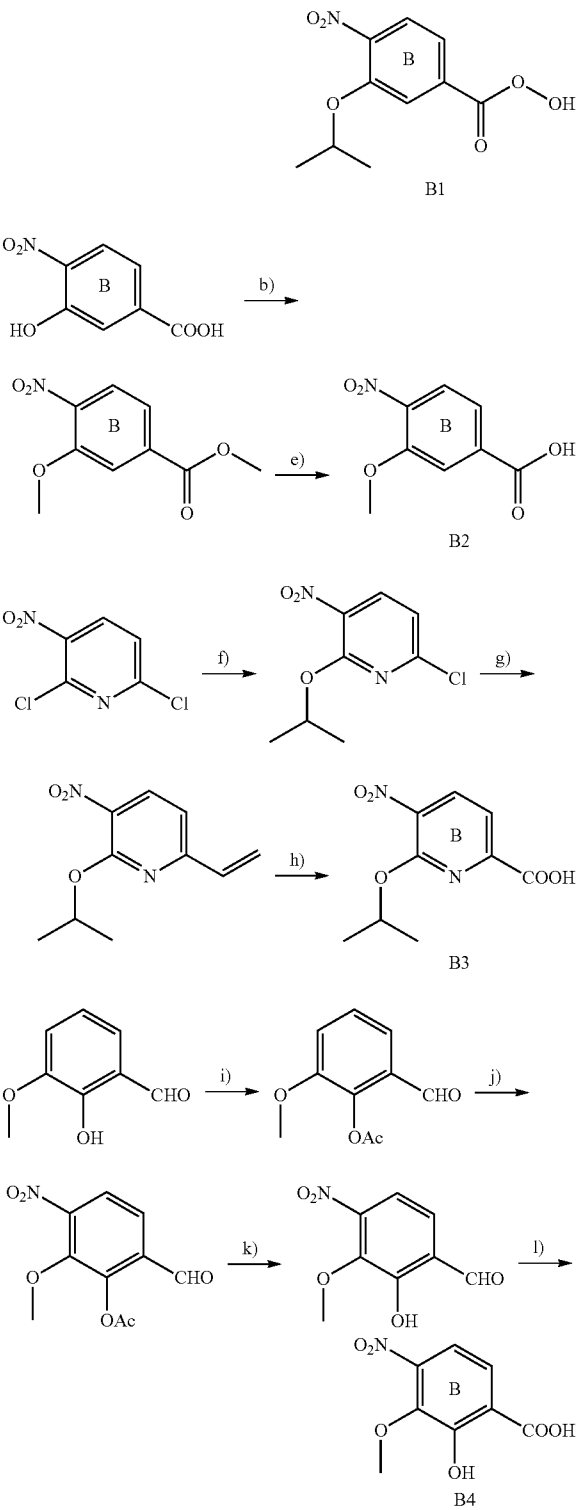
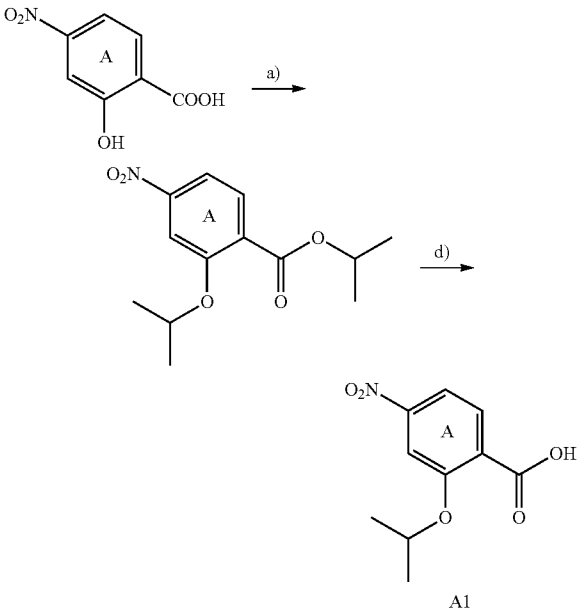


a) $BrCH(CH_3)_2$, K_2CO_3, DMF, 90° C., overnight; b) $SO_2(OMe)_2$, K_2CO_3, DMF, 90° C., overnight; d) NaOH/MeOH, 45° C., overnight; e) KOH, $MeOH/H_2O$; f) i-PrOH/NaH; g) $H_2C{=}CHSn(Bu)_3$, $Pd[(Ph)_3P]_4$; h) $KMnO_4$; i) AcCl/pyridine; j) KNO_3/TFAA, k) NaOH, l) $AgNO_3$/NaOH

Preparation of Ring A

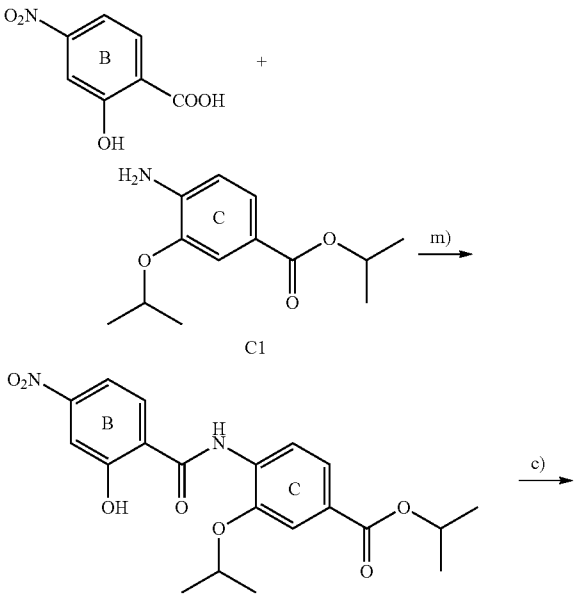
[0549]



a) $BrCH(CH_3)_2$, K_2CO_3, DMF, 90° C., overnight; d) NaOH/MeOH, 45° C., overnight

1.2. Coupling of Ring B and C to Give the Different Prepared BC Fragments

[0550]



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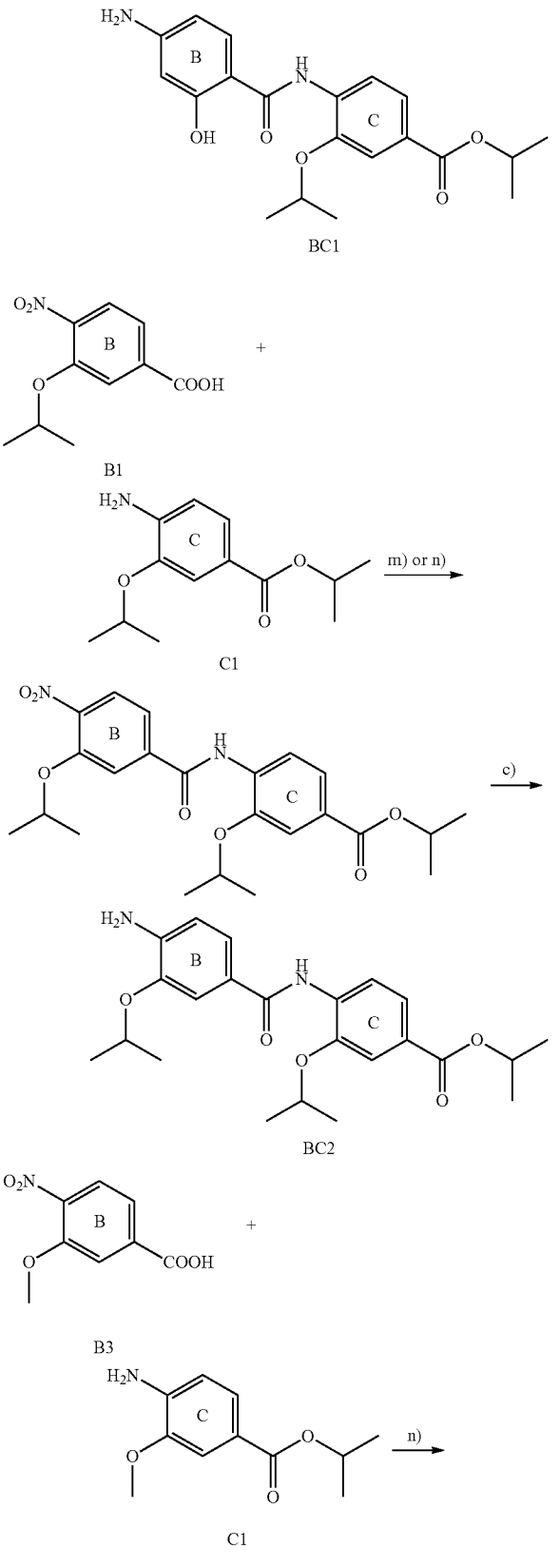

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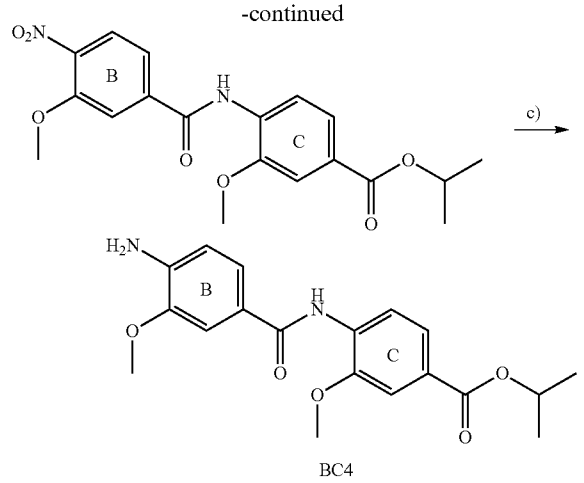
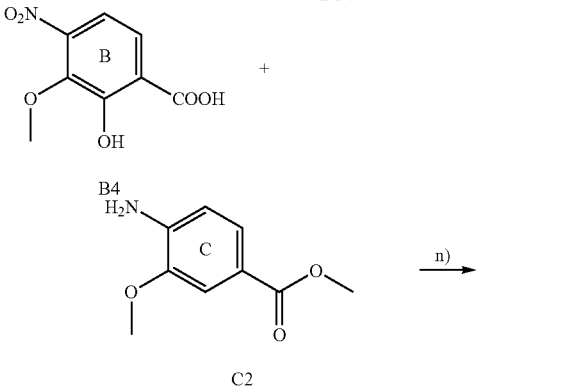
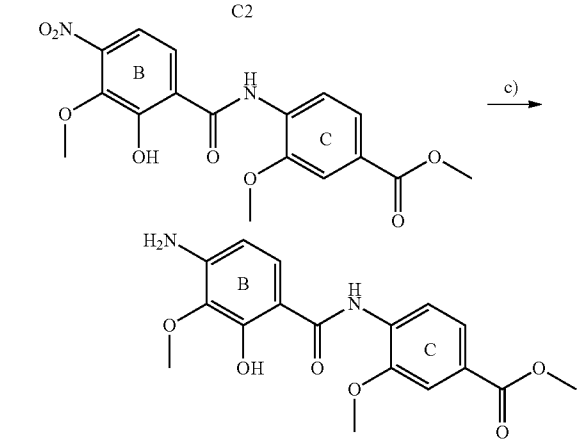


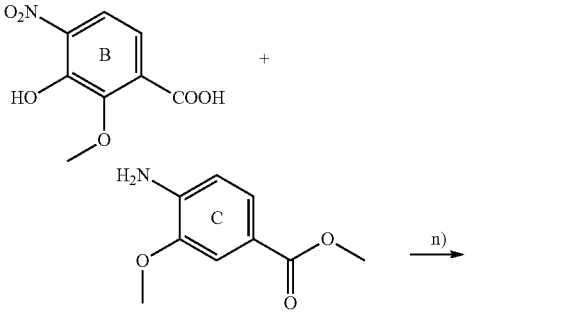
BC4



C2



BC5



C2

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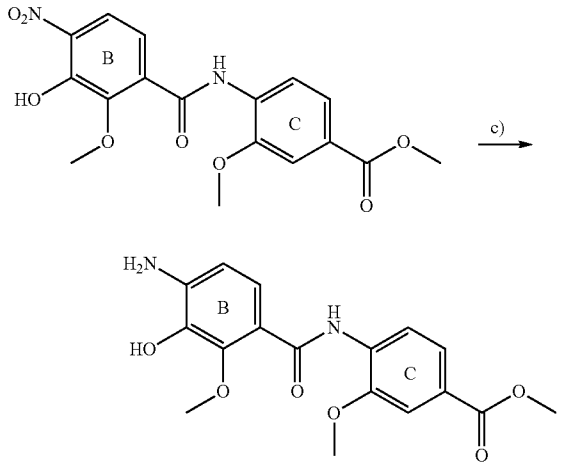
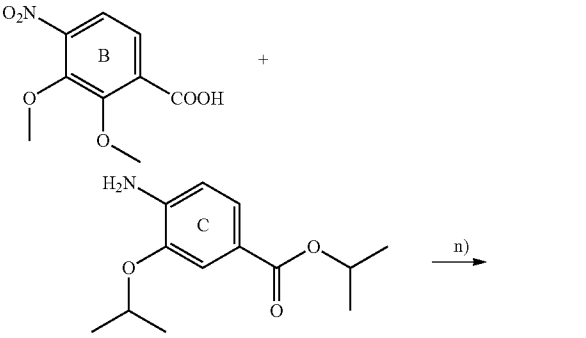
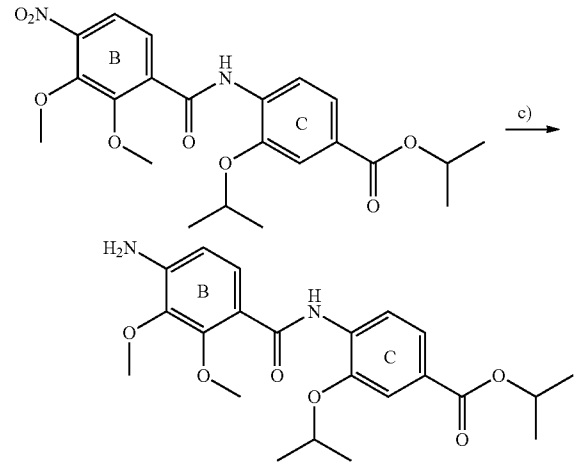


BC6



C1

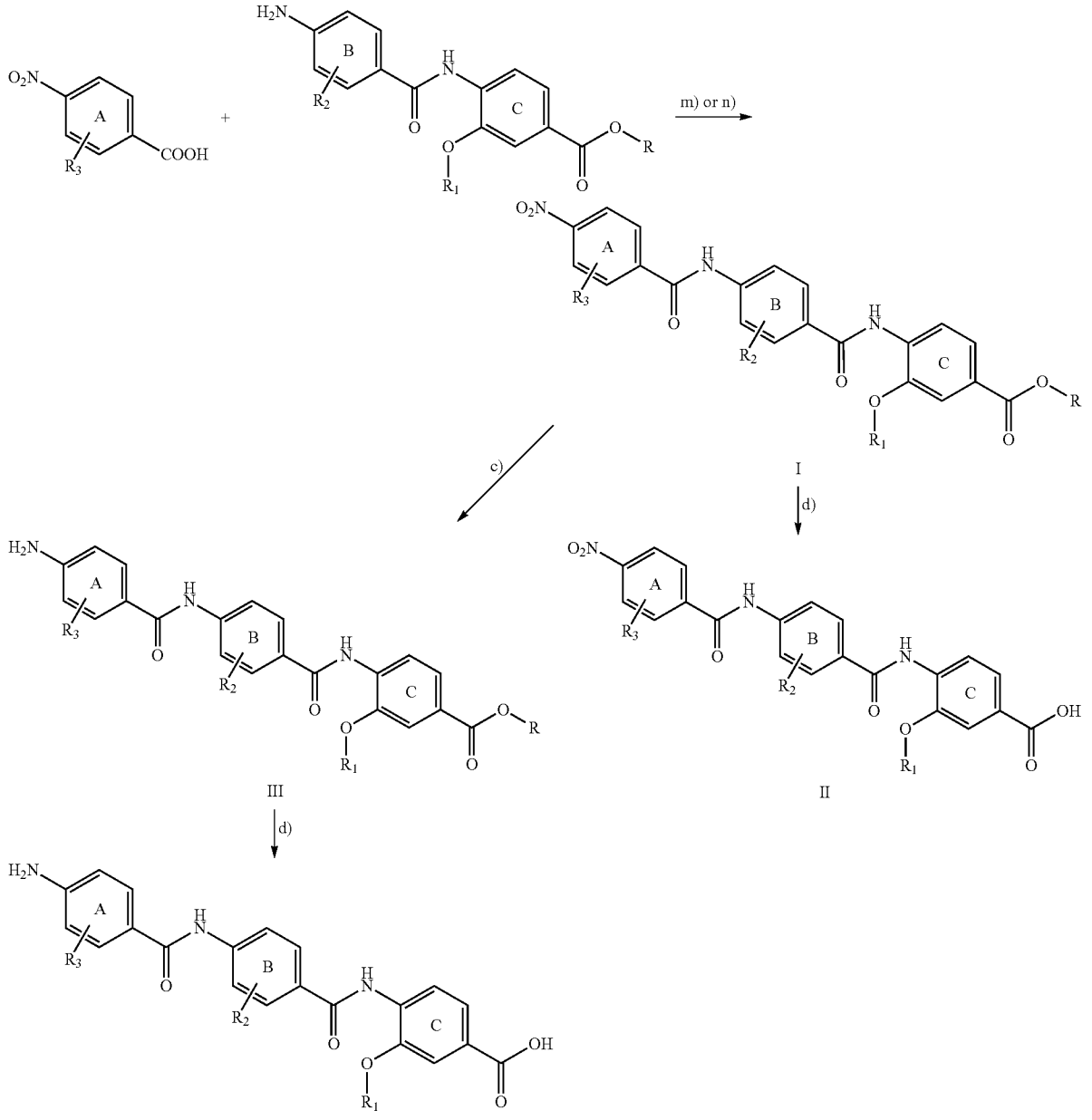


BC7

c) Fe, NH_4Cl, $EtOH/H_2O$, reflux, 2 hours; m) PCl_3, CH_2Cl_2, Xylene, 145° C., 2 hours; n) Cl_2PPh_3, $CHCl_3$; o) EDC, HOBT

1.3. Coupling of Ring a with BC Fragments

[0551] 1.3.1. Coupling of Ring A with BC Fragments (BC1, BC2, BC3, BC5, BC6, BC7) to Synthesize the Cystobactamide C Derivatives (1a)-(23a)



c) Fe, NH_4Cl, $EtOH/H_2O$, reflux, 2 hours; d) NaOH/MeOH, 45° C., overnight; m) PCl_3, CH_2Cl_2, Xylene, 145° C., 2 hours; n) Cl_2PPh_3, $CHCl_3$

Compound	Scaffold	R	R_1	R_2	R_3
(1a)	I	iPr	iPr	2-OH	H
(2a)	I	iPr	iPr	2-OH	2-OH
(3a)	I	iPr	iPr	2-OH	2-OiPr
(4a)	I	iPr	iPr	2-OH	2-F
(5a)	I	iPr	iPr	3-OiPr	2-OH
(6a)	II	—	iPr	2-OH	H
(7a)	II	—	iPr	2-OH	2-OH
(8a)	II	—	iPr	2-OH	2-OiPr
(9a)	II	—	iPr	2-OH	2-OMe
(10a)	II	—	iPr	3-OiPr	2-OH

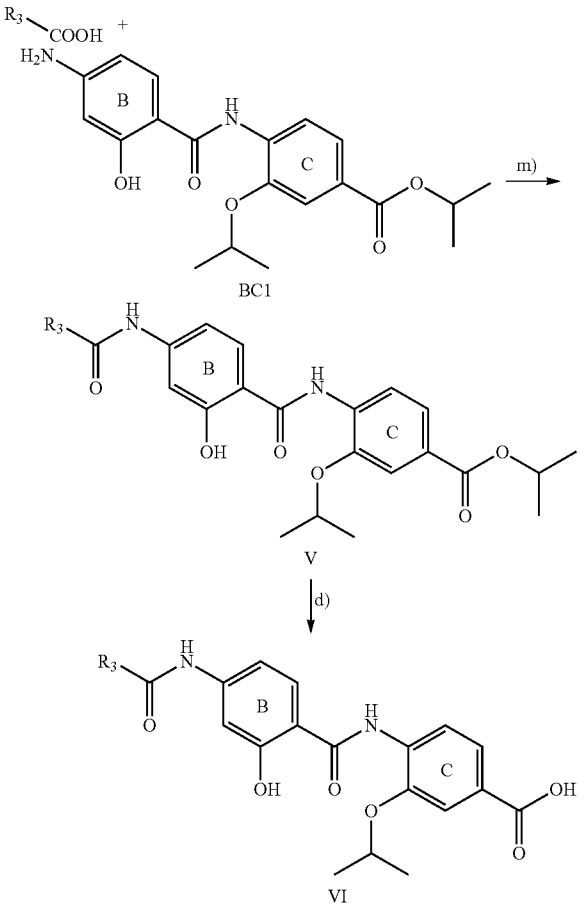
-continued

Compound	Scaffold	R	R_1	R_2	R_3
(11a)	III	iPr	iPr	2-OH	H
(12a)	III	iPr	iPr	2-OH	2-OH
(13a)	III	iPr	iPr	2-OH	2-OiPr
(14a)	III	iPr	iPr	3-OiPr	2-OH
(15a)	IV	—	iPr	2-OH	H
(16a)	IV	—	iPr	2-OH	2-OH
(17a)	IV	—	iPr	2-OH	2-OiPr
(18a)	IV	—	iPr	3-OiPr	H
(19a)	IV	—	Me	3-OMe	H

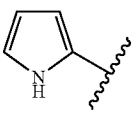
-continued

Compound	Scaffold	R	R_1	R_2	R_3
(20a)	II	—	Me	2-OH, 3OMe	H
(21a)	IV	—	Me	2-OH, 3OMe	H
(22a)	IV	—	Me	2-OMe, 3OH	H
(23a)	IV	—	iPr	2,3-diOMe	H

1.3.2. Coupling of Ring a with BC1 Fragment to Synthesize the Cystobactamide C Derivatives (24a)-(31a)



d) NaOH/MeOH, 45° C., overnight; m) PCl_3, CH_2Cl_2, Xylene, 145° C., 2 hours

Compound	Scaffold	R3
(24a)	V	

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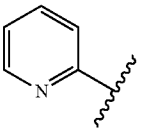
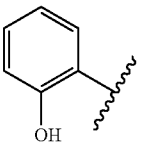
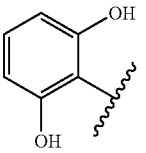
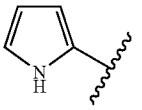
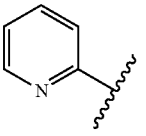
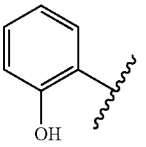
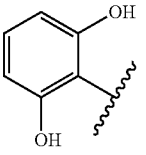
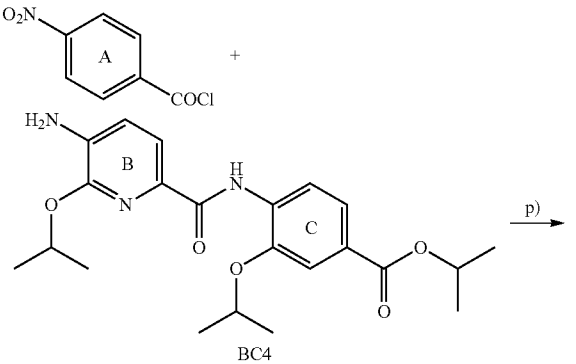
Compound	Scaffold	R3
(25a)	V	
(26a)	V	
(27a)	V	
(28a)	VI	
(29a)	VI	
(30a)	VI	
(31a)	VI	

1.3.3. Coupling of Ring a with BC4 Fragment to Synthesize the Cystobactamide C Derivatives (32a)-(33a)



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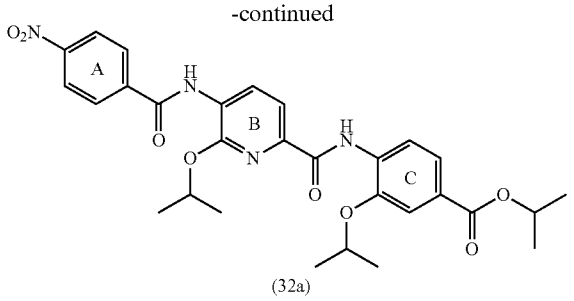
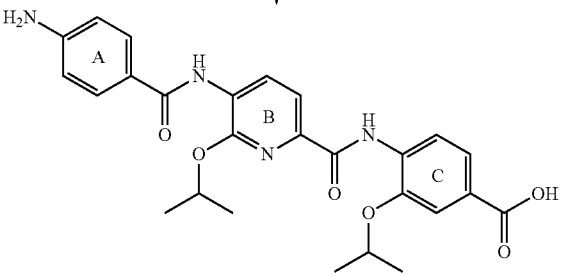


(32a)



(33a)

d) NaOH/MeOH, 45° C., overnight; p) CH_2Cl_2, pyridine, rt, overnight

2. EXPERIMENTAL

2.1. General Experimental Information

[0552] Starting materials and solvents were purchased from commercial suppliers, and used without further purification. All chemical yields refer to purified compounds, and not optimized. Reaction progress was monitored using TLC Silica gel 60 F_{254} aluminium sheets, and visualization was accomplished by UV at 254 nm. Flash chromatography was performed using silica gel 60 Å (40-63 μm). Preparative RP-HPLC was carried out on a Waters Corporation setup contains a 2767 sample manager, a 2545 binary gradient module, a 2998 PDA detector and a 3100 electron spray mass spectrometer. Purification was performed using a Waters XBridge column (C18, 150×19 mm, 5 μm), a binary solvent system A and B (A=water with 0.1% formic acid; B=MeCN with 0.1% formic acid) as eluent, a flow rate of 20 mL/min and a gradient of 60% to 95% B in 8 min were applied. Melting points were determined on a Stuart Scientific melting point apparatus SMP3 (Bibby Sterilin, UK), and are uncorrected. NMR spectra were recorded either on Bruker DRX-500 (^{1}H, 500 MHz; ^{13}C, 126 MHz), or Bruker Fourier 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer at 300 K. Chemical shifts are recorded as 6 values in ppm units by reference to the hydrogenated residues of deuterated solvent as internal standard ($CDCl_3$: δ=7.26, 77.02; DMSO-d_6: 6=2.50, 39.99). Splitting patterns describe apparent multiplicities and are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet). Coupling constants (J) are given in Hertz (Hz). Purity of all compounds used in biological assays was 95% as measured by LC/MS Finnigan Surveyor MSQ Plus (Thermo Fisher Scientific, Dreieich, Germany). The system consists of LC pump, autosampler, PDA detector, and single-quadrupole MS detector, as well as the standard software Xcalibur for operation. RP C18 Nucleodur 100-5 (125×3 mm) column (Macherey-Nagel GmbH, Dühren, Germany) was used as stationary phase, and a binary solvent system A and B (A=water with 0.1% TFA; B=MeCN with 0.1% TFA) was used as mobile phase. In a gradient run the percentage of B was increased from an initial concentration of 0% at 0 min to 100% at 15 min and kept at 100% for 5 min. The injection volume was 10 μL and flow rate was set to 800 μL/min. MS (ESI) analysis was carried out at a spray voltage of 3800 V, a capillary temperature of 350° C. and a source CID of 10 V. Spectra were acquired in positive mode from 100 to 1000 m/z and at 254 nm for UV tracing.

2.2. LC/MS Data for the Triaryl Derivatives

[0553]

Compound	LC/MS m/z (ESI+)
(1a)	521.99 $[M + H]^+$
(2a)	537.87 $[M + H]^+$
(3a)	579.90 $[M + H]^+$
(4a)	540.07 $[M + H]^+$
(5a)	580.11 $[M + H]^+$
(6a)	479.98 $[M + H]^+$
(7a)	496.02 $[M + H]^+$
(8a)	537.99 $[M + H]^+$
(9a)	509.98 $[M + H]^+$
(10a)	538.11 $[M + H]^+$
(11a)	492.02 $[M + H]^+$
(12a)	508.01 $[M + H]^+$
(13a)	550.02 $[M + H]^+$
(14a)	550.13 $[M + H]^+$
(15a)	449.87 $[M + H]^+$
(16a)	465.93 $[M + H]^+$
(17a)	508.07 $[M + H]^+$
(18a)	492 $[M + H]^+$
(19a)	435 $[M]^+$
(20a)	482 $[M + H]^+$
(21a)	452 $[M + H]^+$
(22a)	452 $[M + H]^+$
(23a)	494 $[M + H]^+$
(24a)	466.20 $[M + H]^+$
(25a)	478.07 $[M + H]^+$
(26a)	493.17 $[M + H]^+$
(27a)	509.12 $[M + H]^+$
(28a)	423.53 $[M + H]^+$
(29a)	436.13 $[M + H]^+$
(30a)	451.10 $[M + H]^+$
(31a)	467.11 $[M + H]^+$
(32a)	535 [M + H]+
(33a)	493 [M + H]+

2.3 General Synthetic Procedures

[0554] a) A mixture of the acid (25 mmol), isopropyl bromide (52 mmol) and potassium carbonate (52 mmol) in 100 ml DMF were heated overnight at 90° C. Excess DMF was then removed under reduced pressure and the remaining residue was partitioned between water and ethyl acetate. The organic layer was dried over sodium sulphate and the excess solvent was then removed under reduced pressure to give the pure product.

[0555] c) To a stirred solution of the nitro derivative (10 mmol) in EtOH (60 mL), iron powder (2.80 g, 50 mmol) was added at 55° C. followed by NH_4Cl (266 mg, 5 mmol) solution in water (30 mL). The reaction was refluxed for 1-2 h, then iron was filtered while hot and the filtrate was concentrated under vacuum till dryness. The residue was diluted with water (30 mL) and basified by $NaHCO_3$ (saturated aqueous

solution) to pH 7-8. The mixture was extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), and the solvent was removed by vacuum distillation. The obtained crude material was triturated with n-hexane, and collected by filtration.

[0556] d) Ester hydrolysis was done according to the following reported procedure.[1] The ester (0.1 mmol), sodium hydroxide 1M (3 mL) and anhydrous methanol were heated overnight at 45° C. On cooling, the reaction mixture was acidified to pH 1 (3 mL, hydrochloric acid 1 M) and extracted with dichloromethane (3×150 mL). The organic was dried over sodium sulphate and the solvent removed under reduced pressure to leave give the pure product.

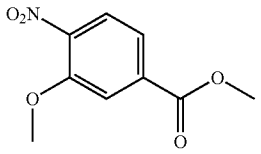
[0557] m) Amide formation was done according to the following reported procedure.[2] A boiling solution of the acid (1 mmol) and the amine (1 mmol) in xylenes 2.5 ml was treated with a 2M solution of PCl_3 in CH_2Cl_2 (0.4 mmol). After 2 hours the excess solvent was evaporated and the residue was purified using column chromatography.

[0558] n) To a stirred solution of the acid (2 mmol), amine (2.4 mmol) in anhydrous $CHCl_3$ (50 mL) under a nitrogen atmosphere, dichlorotriphenylphosphorane (3.0 g, 9 mmol) was added. The reaction was heated at 80° C. for 5 h. Solvent was removed by vacuum distillation. The residue was then purified using flash chromatography.

2.4 Specific Synthetic Procedures

Methyl 3-methoxy-4-nitrobenzoate

[0559]

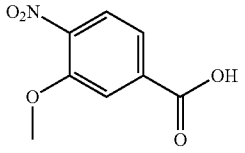


[0560] To a stirred mixture of 3-hydroxy-4-nitrobenzoic acid (9.16 g, 50 mmol) and K_2CO_3 (15.2 g, 110 mmol) in DMF (150 mL), dimethyl sulfate (25.2 g, 200 mmol) was added portion wise then the reaction was stirred at 90° C. overnight. After cooling the mixture was poured on to ice cooled water (400 mL), the precipitate was filtered, washed with cold water then n-hexane.

[0561] Yield 95% (pale yellow solid), m/z (ESI+) 212 $[M+H]^+$.

3-Methoxy-4-nitrobenzoic acid

[0562]

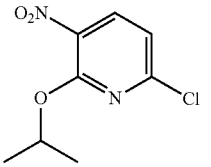


[0563] To a stirred solution of methyl 3-methoxy-4-nitrobenzoate (2.11 g, 10 mmol) in MeOH (30 mL), KOH (1.68 g, 30 mmol) in water (30 mL) was added. The reaction was refluxed for 2 h then MeOH was evaporated by vacuum distillation. The residue was diluted with water (20 mL). The solution was cooled in an ice bath and acidified by $KHSO_4$ (saturated aqueous solution) to pH 3-4. The precipitated solid was collected by filtration, washed with cold water then n-hexane.

[0564] Yield 96% (off-white solid), m/z (ESI+) 198 $[M+H]^+$.

6-Chloro-2-isopropoxy-3-nitropyridine

[0565]

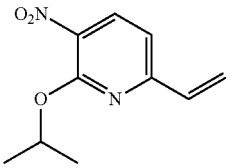


[0566] To a stirred solution of 2,6-dichloro-3-nitropyridine (3.86 g, 20 mmol) in toluene (30 mL), isopropanol (1.44 g, 24 mmol) was added. The mixture was stirred at 0° C. for 15 min. then NaH (50-60% in mineral oil, 1.22 g, 28 mmol) was added portion wise under a nitrogen atmosphere, and the reaction was allowed to stir at room temperature overnight. The reaction was quenched with brine, then diluted with water and extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), and the solvent was removed by vacuum distillation. The residue was dissolved in toluene and purified using flash chromatography (SiO_2, n-hexane-EtOAc=5:1).

[0567] Yield 70% (yellowish white crystals), m/z (ESI+) 217 $[M+H]^+$.

2-Isopropoxy-3-nitro-6-vinylpyridine

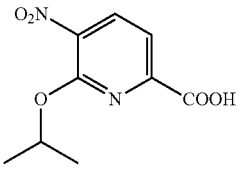
[0568]



[0569] To a stirred solution of 6-chloro-2-isopropoxy-3-nitropyridine (650 mg, 3 mmol), and tributyl(vinyl)tin (1.0 g, 3.15 mmol) in toluene (20 mL) under a nitrogen atmosphere, tetrakis(triphenylphosphine) palladium(0) (180 mg, 5% eq.) was added. The reaction was refluxed overnight. Brine was added, and the reaction was extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), and the solvent was removed by vacuum distillation. The crude product was used directly in the next step without further purification. Yield 90% (yellow liquid), m/z (ESI+) 208 $[M]^+$.

6-Isopropoxy-5-nitropyridine-2-carboxylic acid

[0570]

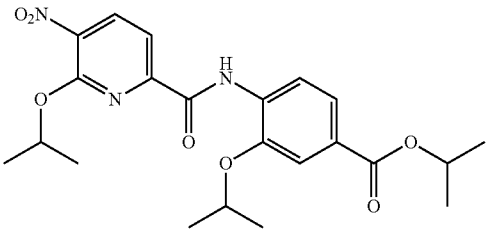


[0571] To a stirred solution of 2-isopropoxy-3-nitro-6-vinylpyridine (625 mg, 3 mmol) in acetone (10 mL), $KMnO_4$ (1.9 g, 12 mmol) solution in 50% aq. acetone (50 mL) was added. The reaction was stirred at room temperature for 24 h. NaOH 0.5 M (5 mL) was added, then the mixture was filtered and filtrate was concentrated under vacuum. The residue was cooled in an ice bath and carefully acidified by $KHSO_4$ (saturated aqueous solution) to pH 4-5, then extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), and the solvent was removed by vacuum distillation. The obtained crude material was triturated with n-hexane, and collected by filtration.

[0572] Yield 75% (beige solid), m/z (ESI+) 227 $[M+H]^+$.

Isopropyl 3-isopropoxy-4-{[(6-isopropoxy-5-nitropyridin-2-yl)carbonyl]amino}benzoate

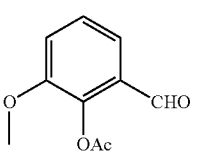
[0573]



[0574] To a stirred solution of 6-isopropoxy-5-nitropyridine-2-carboxylic acid (226 mg, 1 mmol), and isopropyl 4-amino-3-isopropoxybenzoate (237 mg, 1 mmol) in a mixture of anhydrous $CHCl_3$ (50 mL) and DMF (1 mL) under a nitrogen atmosphere, HOBt (676 mg, 5 mmol) was added at 0° C. followed by EDC.HCl (958 mg, 5 mmol). The reaction was allowed to stir at 0° C. for 2 h. then at room temperature overnight. Solvent was removed by vacuum distillation. The residue was dissolved in toluene and purified using flash chromatography (SiO_2, n-hexane—EtOAc=2:1). Yield 70% (pale yellow solid), m/z (ESI+) 446 $[M+H]^+$.

2-formyl-6-methoxyphenyl acetate

[0575]

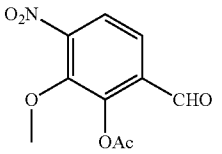


[0576] To a stirred solution of 3-methoxysalicylaldehyde (4.56 g, 30 mmol), and pyridine (2.43 mL, 30 mmol) in DCM (40 mL), acetyl chloride (2.36 g, 30 mmol) was added drop wise. The reaction was stirred at room temperature overnight then the solvent was removed by vacuum distillation. The residue was triturated in cold dil. HCl and filtered, washed with cold water then n-hexane.

[0577] Yield 94% (off-white solid), m/z (ESI+) 195 $[M+H]^+$.

6-formyl-2-methoxy-3-nitrophenyl acetate

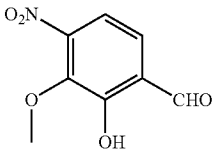
[0578]



[0579] To a stirred ice-cooled suspension of 2-formyl-6-methoxyphenyl acetate (1.94 g, 10 mmol), and KNO_3 (1.01 g, 10 mmol) in $CHCl_3$ (15 mL), trifluoroacetic anhydride (12 mL) was added. The reaction was stirred in an ice bath for 2 h. then at room temperature overnight. The reaction was diluted very carefully with water (50 mL) and extracted with $CHCl_3$. The combined organic extract was dried ($MgSO_4$), and the solvent was removed by vacuum distillation. The residue was dissolved in toluene and purified using flash chromatography (SiO_2, n-hexane—EtOAc=3:1). Yield 45% (yellow semisolid), m/z (ESI+) 239 $[M]^+$.

2-hydroxy-3-methoxy-4-nitrobenzaldehyde

[0580]

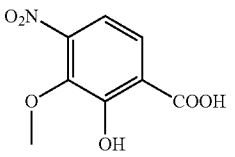


[0581] To a stirred suspension of 6-formyl-2-methoxy-3-nitrophenyl acetate (957 mg, 4 mmol) in water (30 mL), NaOH (0.8 g, 20 mmol) was added. The reaction was refluxed for 2 h then allowed to stir at room temperature overnight. The solution was cooled in an ice bath and acidified by HCl 2 M to pH 3-4. The precipitated solid was collected by filtration, washed with cold water then n-hexane.

[0582] Yield 90% (yellowish brown solid), m/z (ESI+) 197 $[M]^+$.

2-hydroxy-3-methoxy-4-nitrobenzoic acid

[0583]

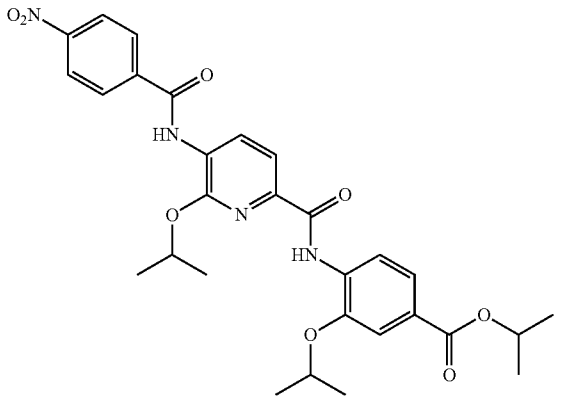


[0584] To a stirred solution of 2-hydroxy-3-methoxy-4-nitrobenzaldehyde (788 mg, 4 mmol), and NaOH (0.8 g, 20 mmol) in water (50 mL), $AgNO_3$ (3.4 g, 20 mmol) was added portion wise. The reaction was refluxed overnight, then allowed to cool and filtered through celite. Filtrate was cooled in an ice bath and acidified with HCl 37% to pH 3-4. The precipitated solid was collected by filtration, washed with cold water then n-hexane.

[0585] Yield 65% (beige solid), m/z (ESI+) 213 $[M]^+$.

Isopropyl 3-isopropoxy-4[({6-isopropoxy-5-[(4-nitrobenzoyl)amino]pyridin-2-yl}carbonyl)amino] benzoate

[0586]



[0587] To a stirred solution of isopropyl 4-{[(5-amino-6-isopropoxypyridin-2-yl)carbonyl]amino}-3-isopropoxybenzoate (207 mg, 0.5 mmol), and pyridine (0.1 mL) in DCM (20 mL), 4-nitrobenzoyl chloride (185 mg, 1 mmol) was added. The reaction was stirred at room temperature overnight then the HCl 2 M (20 mL) was added. The mixture was extracted with DCM then EtOAc. The combined organic extract was dried ($MgSO_4$), and the solvent was removed by vacuum distillation. The residue was dissolved in toluene and purified using flash chromatography (SiO_2, n-hexane—EtOAc=1:1). Yield 80% (yellow crystals), m/z (ESI+) 565 $[M+H]^+$.

5. REFERENCES

[0588] 1) Valeria Azzarito, Panchami Prabhakaran, Alice I. Bartlett, Natasha Murphy, Michaele J. Hardie, Colin A. Kilner, Thomas A. Edwards, Stuart L. Warriner, Andrew J. Wilson. 2-O-Alkylated Para-Benzamide α-Helix Mimetics: *The Role of Scaffold Curvature*. Org. Biomol. Chem., 2012, 10, 6469.

[0589] 2) Alina Fomovska, Richard D. Wood, Ernest Mui, Jitenter P. Dubey, Leandra R. Ferreira, Mark R. Hickman, Patricia J. Lee, Susan E. Leed, Jennifer M. Auschwitz, William J. Welsh, Caroline Sommerville, Stuart Woods, Craig Roberts, and Rima McLeod. *Salicylanilide Inhibitors of Toxoplasma gondii*. J. Med. Chem., 2012, 55 (19), pp 8375-8391.

6. ACTIVITY OF THESE COMPOUNDS

[0590] Several of these compounds were tested for their activity against an *E. coli* strain (TolC-deficient) according to the procedures described above. Most tested compounds showed an activity (MIC) of from 1 to 320 μM.

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<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(3072)
<223> OTHER INFORMATION: CysL

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<211> LENGTH: 117
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(117)
<223> OTHER INFORMATION: CysM

<400> SEQUENCE: 14

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acggtcatgc ggaccgtgcc gctcaaggac gccggctccg gcgacagggc ttgttag 117

<210> SEQ ID NO 15
<211> LENGTH: 1074
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1074)
<223> OTHER INFORMATION: CysN

<400> SEQUENCE: 15

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agatgcttga tggatatcct ggaccgcggg gatcctcgcc tcttcgtcat cgtggggccc 180

tgctccattc acgatccggt ggcggggctg gactatgcga agcggctgcg gaaactcgct 240

gatgaggttc gcgagaccct gttcgtggtg atgcgcgtgt acttcgaaaa gccgcgcacc 300

accacgggtt ggaaaggctt catcaatgac ccgcgcatgg atggctcttt ccacatcgag 360

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gccaccgagg cgctggaccc catcgcgtcg cagtactacg gcgacctcat ttcctggacg 480

gccattggcg cgcgcaccgc cgagtcgcag acgcaccgcg agatggcgtc cggcctttcc 540

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<210> SEQ ID NO 16
<211> LENGTH: 612
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(612)
<223> OTHER INFORMATION: CysO

<400> SEQUENCE: 16

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cggcggtgca agttgcccga aagccgctgg gtccggagcc gcctggagga ttgtgtattc 180

gagggatgcg atctcctgcg gatggtaccg gagaagctcg cgctgcgaag cgtgaccttc 240

aaagacaccc gcctcatggg cgtggactgg agtggactcg gaaccatgcc ggacgtccag 300

ttcgaacagt gcgatctgcg ctacagctcc ttcttgaagt tgaatctacg caagacgcgg 360

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<210> SEQ ID NO 17
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<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(702)
<223> OTHER INFORMATION: CysP

<400> SEQUENCE: 17

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gcgattgccc gcggcgcacc cgcccattgg ctgggttacg tcggcgtcga ggacgtcgat 180

gaagcggtgc gctcgttcgt ggggcgcggg gcgacccagc tcggcccgac ccacccgacg 240

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gcgaacgtgc aacagacggc cgcctcgtat tgcgacctgt tcggatggcg gctctcggat 420

cgccgcgacc ttggtgcgct gggggttcac caggagttca cctggcgctc ggacgagccg 480

agcgccggct cggtcgtgga cgtggcgggg ctcaaggggg tccattcaca ctggctgttc 540

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gtcatcggcc ccatggaact tccgaatggc gatcgcatcg ccgtgtgcga ggatccgcaa 660

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<210> SEQ ID NO 18
<211> LENGTH: 795
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(795)
<223> OTHER INFORMATION: CysQ

<400> SEQUENCE: 18

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<210> SEQ ID NO 19
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<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1002)
<223> OTHER INFORMATION: CysR

<400> SEQUENCE: 19

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cgccacgcgg tcctcttcat gaacgtgctc aagctggtgt ggagtgagat ggaggagagc 720

gcccggctcg ccatcggtca gctgctgcca gagttcatcc gcgagtacct cagcccgaag 780

atgatggcgg agtacgagcg cgtcgtgctg gagcagctcg gtctagcggc cgagcacatc 840

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<210> SEQ ID NO 20
<211> LENGTH: 1929
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1929)
<223> OTHER INFORMATION: CysS

<400> SEQUENCE: 20

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gatgccgatg tctacgcgat ctcttgctat gtctggaaca tgggcttcgt gaagcggtgg 240

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gcgcgcatcc aggatctgaa cacggtccca tctccctacc tggaaggcta cttcgacagc 540

gagaagtacg tgtgggcgcc ccttgagacg aaccggggat gcccctacca gtgcacctac 600

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<210> SEQ ID NO 21
<211> LENGTH: 3804
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(3804)
<223> OTHER INFORMATION: CysT

<400> SEQUENCE: 21

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accctgaaga acgtccccgg ctacgacaat ccgaactggg gcgcctcctg gaaggaccgc 480

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cagtgggccg tcatcggcga caaccacttc tcccgcaccc tcaaggacta cccctacctc 780

aacgatccgg gctccgacac gctcgtctcc ccgcccaacc gcgccgatct ccagaacacc 840

agctccgtgg gctcctgggt gagcgcccag atggcccacg agcagcaggt catcaagaac 900

aagtaccct tcgcctccac tccccactgg gtgcgctacg tggaccccgc cacgggcgcc 960

gagtcgcgcg tcgtcggcat ccccgtcaac cagaacggct cctggctcga gggctgggaa 1020

ggcgaggcca ccgtcgacgt cgtcaacctc aagagcttcg agggcctcgt tccccagcgg 1080

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gagtacctcg tccaccacac ccccgcctcc accgacgtgg tgcacgtcca ggacggctcg 1260

tgggtggaca cgcgcgactc ctcctcggat ccccagtggc accactggaa gctgcccttc 1320

ggcatctgga agggtcagtt ccccgccttc aacgccgcca ccggcctcaa tctctctccc 1380

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aagacgaacc tcagcggcgt gcaggagggc atgacggtct ccctcgagca cggctggcac 1440

tacctcgagc gcaacttcgc cctgctccag gccgccctca actacgcgaa gaccgccgag 1500

cagatctggc tcgacgcgca ccccaatcac tggtcgccca ccaccgcgat cgacaagcag 1560

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gccaacaccg acaagtccga gggctggacg ctccacttct tcaacaacca cttcgccctc 1920

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acccacaaga gcatcgaccc gctcgacaac acccacaagg tctatgatcc ggcggcgcgc 2040

aaggccgcgg gtgttcccaa catcgatccg gcccgcgtgg gcgcctgggt ggactacccg 2100

ctcacccggc gcgacctgaa gcctgtcatg aatggtgttt cctggcagcc cgcctacctg 2160

cccgtcatgg ccaaggtgcc cgcgcaggag atcggcgacc tctactacgt ctacctgggc 2220

aactaccgcg accagctcct cgactactac atcgaggcca ccgacagccg gggcaacatc 2280

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cagacgggca acagcgccac cgtctactat ttcaacaaca acttcgccct caaatacatc 3000

cacttccgca tcggcggtgg cacgtggacg accgtgcccg gcaacgtcat ggccacctcc 3060

gaggtgccgg gctacgccaa atacaccgtc aatctgggag cggccaccca gctcgagtgt 3120

gtcttcaacg atggcaaggg cacctgggac aacaacaagg gcaacaacta cctcctgccc 3180

gcgggcacct ccacggtgaa ggacggcgtc gtctccagcg gagcgcccgc gctcgacacc 3240

accgcaccct ccgtcccctc gggcctcacg gcggcgtcca agacgtcctc ctccgtgtcg 3300

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tggaacaccg gcgccgccat cctcctgtct ccggccagct acccgaagtg gagcgtgacg 3660

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ctcagcctgc ccggctcgac ggccctcgaa tacaagtaca tcaagaagga cggctccggg 3720

aacgtcacct gggagagcgg cgccaaccgc tcgaccacga tccccgcctc ggggaccgcg 3780

accctcaacg acacctggaa gtag 3804

<210> SEQ ID NO 22
<211> LENGTH: 831
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(831)
<223> OTHER INFORMATION: ORF1

<400> SEQUENCE: 22

gtgccacatc catccgagca gagcgctccg tcgggactcc gggcgcggct gcacgaaatc 60

atcttcgagt cggacacccc ggcgggccgc gccttcgatg tggcattgct gtgggccatc 120

gtgctcagcg tcctcgcggt gatgctcgag agcgtggagt ccatcagcgt ccagcatggg 180

cagaccatcc gcgtcctcga gtggtgtttc accgggctct tcacactgga gtacgtgctg 240

cggctgctgt cggtgaaacg gccgctgcgc tatgcgctga gcttcttcgg gctggtggat 300

ctgctggcca tcctgccctc ggtgctgagc ttgatgctgc ccggcatgca gtccctgctg 360

gtggtgcggg tgttccgcct gctgcgcgtc ttccgcgtac tcaagctcgc cagcttcctc 420

ggggaggcgg acgtgctgct caccgcgctc cgggccagtc ggcggaagat catcgtcttc 480

ctcggggcgg tgctgagcac ggtcgtcatc atgggcgcgg tgatgtacat ggtggagggg 540

cgcgccaacg gcttcgacag catcccgcgg gggatgtatt gggccatcgt gacgatgacc 600

acggtgggct acggagacct ctcgcccaag acggtgcccg gacagttcat cgcctcggtg 660

ttgatgatca tgggctacgg catcctcgcg gtgcccacgg gcatcgtgtc cgtggagctc 720

gcccaggcga cccggcagca cgccatcgac ccgcgcgcct gtcccggctg cggcctgcag 780

ggccacgacc tggacgcgca ccactgcaag cactgcggca ccgccctctg a 831

<210> SEQ ID NO 23
<211> LENGTH: 237
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(237)
<223> OTHER INFORMATION: ORF2

<400> SEQUENCE: 23

atggcacagg accaggacag ggagaagctg cattccgacg cggacaagga gaggctgcac 60

ccgaaggtcg actcgggtga cgtctcgggc cggggccgcg agcggcggcc cgacgaggaa 120

taccccaagc agcgcaacgc gggcgagttc ggcacccacg gaggccccaa caagggcggc 180

aaggaagacc ggcggcaact gcatgccccc ggcagctcca aggcgggctc ccagtag 237

<210> SEQ ID NO 24
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(489)
<223> OTHER INFORMATION: ORF3

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<400> SEQUENCE: 24

atgggaagaa cctacagttt cgaacccttc ttgtcgcagc aacccgcgca gacctacaag 60

ggctcgggtc cccggctcgg caatgaagaa cacaagatcg ccctcaccaa ggaagaggag 120

aaggcggccc tgcctgacac gcccaccggc tatggacagg cccacgccga gaccgtgaag 180

cgctaccgcg cccgcgcgga gaagaagcgc acggagccca agacccccgc tacccgggcg 240

aagaaggccg cccccaaggc gaagcccacc cggaaggtgg cgacgcaaga ggccaccgcc 300

aaggccccta cccgtcaagc gcgggaggag accgagccga aggcccccgc gcgcaagaag 360

ctgagcgcca cggggctcgt gggtagcatc gggcgcaagg tggtgactcg ggccgcggtc 420

gcggcgaaga agaccgtggc gcgcgccgtg aagaccgccg ccgcgcgcaa gtccgcgaag 480

aagcgctga 489

<210> SEQ ID NO 25
<211> LENGTH: 264
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(264)
<223> OTHER INFORMATION: ORF4

<400> SEQUENCE: 25

atgagcccgg caagacgcaa ggagagcaag cagcacgaag tgggctccgc cacacacgca 60

cggcgggtga tcgtggcgac ggatggccgg ggttggtacg tccgattcga gggcaaccgt 120

cagctcggcc ggtattccaa cgtgacccag gccatccacg gcgggcgcag gctggctcgc 180

cagcacaagc ccgcgggcct cgtggtgcgc tacctggacg gggaagagga agagtcctgg 240

tacggggacc gcgaggcgcc ttga 264

<210> SEQ ID NO 26
<211> LENGTH: 450
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(450)
<223> OTHER INFORMATION: ORF5

<400> SEQUENCE: 26

atgaaacaca tcaaggcggt ggtggtgggt gcgttgtccg cggctctgct cttcggcgtg 60

ggatgtcaga cgacgggcgg tgctgggaat caaggaacgg gcgggagcga tacgtctcag 120

ggcggcacca tgaccggaag tgagacgacc ggaaccggaa cgaccggagg caccacggaa 180

ggtggtgaca ccacgggcgg aggcaccggc ggaacaggtg ctggcgacat cgacggttcg 240

agcagtggca gcacgggctc cggtagcgac gtgggcggct ccggcggctc gggcgtgtcc 300

agtgaaccgg gcggtttcag ccccgacgcc tcgggcgtgg acagcgacct gggcggctcc 360

ggcaccggca gtgacgtgga cggctccggc agcacggact ccagcggcaa catgagcggc 420

acgggctccg aagacgacac cagccgctga 450

<210> SEQ ID NO 27
<211> LENGTH: 1578
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1578)
<223> OTHER INFORMATION: ORF6

<400> SEQUENCE: 27

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caggagcgtc ccagcgaggg cgacctcttc ggcggcgaca ctccagagac gaagcccgct 120

ccggccgatg cgccccgccc cgacgagagt tccctcttcg gtgacacccc cgcgtccacc 180

ccggccgcac agagcgcggc ggccaccgcg gccccgaca agccctccgc cacgccccag 240

gaccgggatg cgcaggcgct cggtggcccg tcggccacca acgccttcga caccgaggag 300

gccgtcgagg atccgctgaa gatcggcggc cgcttctacc tgcgcgccta ctcacaggcc 360

aacgaagggg tgtccttcag caacaccacc ttctccgccc ccatgctggt ggacggctac 420

ttcgatgccc gccccaccga gcggctgcgc ggcttcgtgc tcggacggct caccttcgat 480

ccgacccgca aggcgggctc cctcggcatc gtccccacga gcacgtccac ctccaacgtc 540

gctgcggatc cggtcgtgct gttggatcag gcctggctgc gcttcgacct ggaccacaag 600

ctcttcatca ccgtcggcaa gcagcacgtg aagtggggca cctcgcgctt ctggaacccc 660

accgacttcc tctcgcccca gcgcagggat ccgctcgccc tcttggacac gcgcaccggc 720

gcgaccatgc tcaagatgca catgccctgg gaggcgaaag gctggaactt ctacgtcctc 780

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cccatagagg cgtactaccc cgagggttac acgccgcagg tgagcggcgg cgcgacctgg 1140

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aactatggcc agcggggtgg cgagttccgc ttcgcgctca acctgccggc cctgcgcatg 1500

ggcgagcagg tgacgcctcc catcgccgtc gctccaccta ccatccaggc cggggtgggt 1560

ctgcgcatcg acctttga 1578

<210> SEQ ID NO 28
<211> LENGTH: 786
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(786)
<223> OTHER INFORMATION: ORF7

<400> SEQUENCE: 28

atgaccctgc gcaacctcct cggcgccctg ttcgccgcgc tgctgctggc cgctccgacc 60

gctcgcgcgg acctcaccga ccccgccgag atcaagaagc tcctggagac gctcgacaac 120

-continued

cgccagcgca acggcggcga ctacaagtcg ctggtgtata tcgagcagaa ggagaaggac 180

aaaacagacg tcgtgcgcga ggccgtcgtc taccggcgcg acgagaagga tcagctgatg 240

atcctcatga ccaagcccaa gggcgaggcc ggcaagggct acctgcggct ggacaagaac 300

ctctggagct acgacccgaa caccggcaag tgggaccggc gcaccgagcg tgagcgtatc 360

gccggcaccg acagccgccg cgccgacttc gacgagtcgc gcctggccga ggagctcgat 420

ggcaagttcg agggcgagga gaaactcggc aagttcacca cctggaagct cgtcctcacc 480

gccaagccga acgtggacgt cgcctacccc gtggtacacc tgtgggtgga gaaggacacg 540

aacaacatcc tcaagcgcca ggagttcgcc ctttccggcc gcctgatgcg cacctcctac 600

ttccccaagt ggatgaagct cttcagcgag tccaagaagg ccgacgtctg gtacccgcag 660

gagatgcgct tctatgacga ggtggagaag accaactcca ccgtcatcgt cgtgaagagc 720

gtggacctgc gctcgctcga ggagaacatc ttcaccaagg cctggttcga gagcaaaagc 780

cgatga 786

<210> SEQ ID NO 29
<211> LENGTH: 1302
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1302)
<223> OTHER INFORMATION: ORF8

<400> SEQUENCE: 29

atgcaacagc tcctcctcat cgcagtgcgc aacctgggca cccacaagcg ccgtacgctt 60

ctgctgggcg gcgccatcgc cggtgtcacg gccctgctcg tcatcctcat gggcctgtcc 120

aacggcatga aggacacgat gctccggtcc gccaccacgc tggtgaccgg gcacgtcaac 180

gtggctggct tctacaaggt gacggccggc cagtctgcgc ccgtggtgac ctcctacccc 240

aagctgctcg agcagctgcg caaggaagtc cccgagctgg acttctccgt ccagcgcacg 300

cgcggctggg tcaagttggt gagcgagtct ggctccgtgc agacgggaat cggcggcatc 360

gacgtagcgg ccgagactgg catccgcaag gtgctgcagt tgcgggaggg tcggttggaa 420

gacctggcgc aacccaatac cctcctcctc ttcgacgagc aggcgaagcg gctcgaggtc 480

aaggtgggtg acagcgtcac cctctccgcg tccaccatgc gcgggatcag caacaccgtg 540

gacgtacgtg tggtggccat cgccgccaac gtgggcatgc tgagttcctt caacgtcttg 600

gtgcccaacg ccaccctgcg cgccctctac cagctgcgcg aggactccac cggcgccctc 660

atgctccacc tcaaggacat gagcgccatc cccagcgtgc aggcgcgcct ctacaagcgt 720

ctgcccgagt tgggttatca ggtgctggag catgaccccc gggccttctt catgaagttc 780

cagaccgtca accgcgaggc ctggacgggg cagaagctgg acatcaccaa ctgggaggac 840

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ttcgtgctgc tcatcatcat cgcggtgggc atcatgaaca ccctgtggat cgccatccgc 960

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gtgggcatgg gcgtgtgcct gctcatcaac gccgtggacc cctccgtgcc cgtgcccgtc 1140

cagctcttca tcctctccga caagctccac ctcatcgtga agcccggatc ggtgatgaga 1200

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gccatcgcgt tcatcacgct gtgcaccacc ttcatctcgc tcattccctc tttcctcgcc 1260

gcgcggatga agcccatcac ggcgatgcac cacatcgggt ga 1302

<210> SEQ ID NO 30
<211> LENGTH: 2106
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2106)
<223> OTHER INFORMATION: ORF9

<400> SEQUENCE: 30

atgggccaac tcaagctcct gctccaagtg gccctgcgca acttgttcgt gagcaggatc 60

aacctcctca tcggaggcat catcttcttc ggcaccgtgc tggtggtggt gggcggctcc 120

ctcgtcgaca gcgtggacga ggcgatgagc cgcagcatta tcggcagcgt cgccggccac 180

ctccaggtgt actcggccca ctccaaggac gagctctcgc tcttcgggca gatgggccgc 240

gaaccggacc tgagcgcgct ggatgacttc tcgcgcatca agcaactggt acagcagcac 300

cccaacgtga agacggtggt gcccatgggc accggcgcca cgttcatcaa ctcgggaaac 360

accatcgacc tgaccttggc gcgcctgcgc gacctctaca agaaagcagc acagggcgac 420

acacccgaac tccgcgggca gatccacagc ctccaggcgc atgtgcgtca catcatcacc 480

ttgctcgagg aggatatgaa gcggcgcagg gaaatcatcg acgacaagac cacggacccc 540

gcggacgcgg aggccatggc ccgcgcccgt tccgaggcct tctgggcgga cttcgacgag 600

aagccattcg actcgctcga gttcctggag aaccgcatcg ccccgtatat gacggacggg 660

gacatgttgt ccctgcgcta tgtaggcacc gacctggtca acttccagaa gaccttcgac 720

cgcatgcgca tcgtggaggg cacgccggtg cccccggggc accgcggcat gatgctctcc 780

aagttcacct acgagaacga cttcaagctg aagacggcgc accggttgga tctcatcaag 840

gaggcgcgtg ataccaacca caagaccatc gcgatggatc cgcaactcca gcgctgggtg 900

aaggagaacc agacccagac gcgggagatc ctcttccagc tcgacgacct caagacgaag 960

caggccgtgg agcggctcca gcgcgtgctg ggcagccagg agacggacct gggcaagcta 1020

ctgcccgcct tcttcaccat ggatgacgcc aacttcgaca cgcgctacca gcagttctac 1080

tccgagctgg cgacgctgct cgacctgtac cgcatccgca tcggggacga cctcaccatc 1140

accgcattct cgcgcaccgg ctatgtgcag agcgtgaacg tgaagatcta cggcacctac 1200

cagttcgacg ggctggagaa gtccgcggtc gccggagccc tcaacctgct ggacctgatg 1260

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cggatcatct cctggcagaa ggcctccggc acgatcggcc agttcgtcct ggtcgccaag 1680

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atccccgccg gcaacgaggc gctctacttc ttcttctcgg gaccccgcct cttccccagt 1980

ctccacctgt caaacctcgt ggcggccttc gtcatcgtgc tcgtggtgtc cgccctctcc 2040

accttctacc ccgcgtacct cgcgacccgg gtctcgcctc tccaggcgat gcagacggac 2100

gagtga 2106

<210> SEQ ID NO 31
<211> LENGTH: 762
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(762)
<223> OTHER INFORMATION: ORF10

<400> SEQUENCE: 31

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accaagacgt actccctggg taaggtgcag gtgcccgcac tccgaggcgt gacgctagag 120

gtgtacccgg gagagttcat ctccatcgcc ggcccatcgg gcagtggcaa gacgacggcg 180

ctcaatctca tcggctgcgt ggacacggcc tcctcgggcg tggtgagcgt ggatggccag 240

gacaccaaga agctcaccga gcggcagctc acccacttgc ggctgcacac catcggcttc 300

atcttccaga gcttcaacct cgtctcggtg ctcagcgtct tccagaacgt agagttcccc 360

ctgctgctgc agcgcaagct caacgcctcc gagcgccgca cgcgcgtgat gacgctgctg 420

gagcaggtgg gcctggagaa gcacgccaaa caccgcccca atgagctgtc tggaggccag 480

cgccagcgcg tggccgtggc gcgcgctctc gtcacccggc ccaagctggt gctcgccgac 540

gagcccaccg ccaacctcga ctccgtcacc ggccagaaca tcatcgacct gatgaaggag 600

ctcaaccgca aggagggcac caccttcatc ttctccaccc acgacgccaa ggtgatgacc 660

cacgccaacg ccgtggtgcg cctggcggac gggaagatcc tcgaccgcat cacgccggcc 720

gaggcccaga aggtcatggc cgtgagcgag gggggccact aa 762

<210> SEQ ID NO 32
<211> LENGTH: 1194
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1194)
<223> OTHER INFORMATION: ORF11

<400> SEQUENCE: 32

atgccgcaga agttcgtggg gaagtggaag ggcgggcggg tcaagctcgt cgatggtcgg 60

aaggtgtggc tcctcgagaa gatggtctcc ggggcccggt tctcggtctc cttggcggtc 120

tccaacgagg aggacgcgct ggccgagctg gccctgttcc ggcgcgaccg ggacgcctac 180

ctggccaagg tgaaggccga caggtcggag gaagtccagg catccactgt agccggggca 240

gttcctctgt cgggggatgt ggggcctcgg ctcgatgccg attctgtccg ggagttcctc 300

cgacacttga cccagcgggg gcgaacggag ggttaccggc gggacgcccg aacctacctg 360

tcgcaatggg ccgaggttct ggccggaagg gacctgagta ccgtcagcct cctcgagttg 420

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cgccgcgccc tgagccaatg gcccacggcc aggaagatgc ggatcatcac gctcaagagc 480

ttcttctcgt ggctgaggga agaggatcgc ctcaaggctg ctgaagaccc cacgttgtcc 540

ctcaaggtgc cgcccgcggt cgcggagaag gggagacggg ccaaggggta ttcgatggcc 600

caagtggaga agctctacgc ggccatcggc tcccagacgg tgagggacgt gctgtgtctg 660

cgggccaaga ccggcatgca cgactcggag atcgcccgcc tggcatcggg caaggggggaa 720

ctgcgcgtcg tcaatgaccc ctccggcatc gccggtactg cgcggtttct gcacaagaac 780

ggccgcgttc acatcctcag tctggatgcc caggcccttg ctgccgcgca gcggctccag 840

gttcggggca gggcgcccat caggaacacc gtccgggagt ccatcgggta tgcgtcggcg 900

cgcattgggc agtcgcccat ccatcccagc gagctccgcc acagcttcac cacctgggcc 960

acgaatgagg gccaggtcgt gagggcaacc cggggcggag tgccactcga tgtcgttgcc 1020

tcggttcttg gccatcagtc cacacgggcg accaagaagt tctatgacgg gaccgaaatt 1080

cccccgatga tcaccgtccc gctcaagctg catcatccac aggacccagc ggtgatgcag 1140

ctgaggcgta actgctcgcc ggaccccgtc gtgacgagag aggcagaggc gtga 1194

<210> SEQ ID NO 33
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(375)
<223> OTHER INFORMATION: ORF12

<400> SEQUENCE: 33

gtgctcctcg cattcccctc cggcctcctg tcgctggcgc tcctgtccac taccaccgaa 60

atctctgcgg ctcttcccgt ggacgagtgc gagtcggcga gcctgcgcat cgagctgccc 120

gctacgccag ggggaaagcc acccgtggtg tgtctcggtc caggtctgcc cattcatttc 180

cgcttcgact ccgcgctcca acagaagtcc ctgaggattc aggatcgggg ctggttcgag 240

gattgggctt tgggccagca gacgctcgta ctgactcctc acgacaacct ggtggctggg 300

aagcgatctg aagtggaggt gtgcttcgcg gatggtgccg ccccggcgtg cgcttccttc 360

gtgctccggc gctga 375

<210> SEQ ID NO 34
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(339)
<223> OTHER INFORMATION: ORF13

<400> SEQUENCE: 34

atgcacacga aggtgccctc cgtcttcgag gcaacgcccg agtctctcag tgacgtggac 60

taccagttct ggcatgagga cttcccgagg gtgttcgagc ggcagcacat cgacgcgcac 120

gcggtgcccg ccattggcgc gtacttgggc gaggtgctgg tgcgtaacct gggcggcaag 180

tggatacctc gccagaaact cgacgaggcc caggtgctcg tcggcaaccg tgtgtggttg 240

ccgtttgcgc gggctcacca ctacatgcgc tcgtgcgaat cgttgctgga ctactccctc 300

acccagctct accgcgtggc cgagcggtac cggggttga 339

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<210> SEQ ID NO 35
<211> LENGTH: 915
<212> TYPE: DNA
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(915)
<223> OTHER INFORMATION: ORF 14

<400> SEQUENCE: 35

atgaaggtgc tggggcttgg tgacgtgaag tcggaggaca gtctccggct cacttttgag 60

ggtgcgcttg atccgcaggc tgcgcttgag aaagttctcg agccattttt ccaggcgctg 120

gaggaatatg caggcgattg gatgccggaa gtcgtcagtg gcaggcggcg actcaaatac 180

tcccgagcca atatctggaa ggctctggag gagcggcgcg atgaacgaag cacagacacc 240

tggctctacc gcacacagcg gccgacactg gagatgtcgc tgcatctctg gtttccgccg 300

cttccgcccg ctttggacgt aatgactacg gtgcaaccgc tcacccgctt cgcggagaag 360

gagcgctgcc gccaattcgt agaaatggta cgcacctggg cctcttgcta cccggtcact 420

cacgccgcag cccacagcgt ggctgacagg gcgttggcag gtgcgcccga ttttggacgc 480

gatgcgcgga ccgcacggag agacgggttc gacagaatct acgagatctt ctggctcaac 540

gtcttcggcc ccaagttggt ggaagccgtg ggccgcgagc gcatgctgtc cacgccagct 600

caccgggtgg aggaactgcc caatggctcc atcctcctgg tgacgtggcc caccgctgcg 660

gacttcgcgg gcgccgaggc acggcacgca caggcgcgcg cgcacgttca cctccggccg 720

gacctccgct tcgacacggt gctgcgaacc ctgcacgagc gtagcgccgc gctcgctccc 780

gttgagccct gcttccaccc ggatgtagcg ccactcctct ctcacgtggt ggatagcgtc 840

gccatccgga tgtggaaaac ctggagcgcg ctaacgagca ttacagaact ctggctgagc 900

acctcgtggc gctga 915

<210> SEQ ID NO 36
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(32)
<223> OTHER INFORMATION: CysL KO For

<400> SEQUENCE: 36

tgattgattg atcggcgcga ttcggcctct gg 32

<210> SEQ ID NO 37
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(32)
<223> OTHER INFORMATION: CysL KO Rev

<400> SEQUENCE: 37

tcaatcaatc atcgggtcgc ggtctcaggc tc 32

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<210> SEQ ID NO 38
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(37)
<223> OTHER INFORMATION: CysK KO For

<400> SEQUENCE: 38

tgattgattg aaaaacagtc ggaggagttt cttgtcc 37

<210> SEQ ID NO 39
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(32)
<223> OTHER INFORMATION: CysK KO Rev

<400> SEQUENCE: 39

tcaatcaatc aactcccagt gccctcagcc tc 32

<210> SEQ ID NO 40
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(70)
<223> OTHER INFORMATION: CysA

<400> SEQUENCE: 40

Met Ser Met Asn Gly Asp Glu Ala Glu Tyr Val Val Leu Ile Asn Gly
1 5 10 15

Glu Glu Gln Tyr Ser Leu Trp Pro Val His Arg Glu Ile Pro Gly Gly
20 25 30

Trp Lys Thr Val Gly Pro Lys Gly Ser Lys Glu Thr Cys Gln Ser Tyr
35 40 45

Ile Gln Glu Val Trp Thr Asp Met Arg Pro Lys Ser Leu Arg Glu Ala
50 55 60

Leu Thr Arg Ser Asn Cys
65 70

<210> SEQ ID NO 41
<211> LENGTH: 317
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(317)
<223> OTHER INFORMATION: CysB

<400> SEQUENCE: 41

Met Ser Thr Pro Ala Ala Gly Ala Lys Pro Ser Tyr Leu Ala Gly Ile
1 5 10 15

Glu Thr Val Met Val Glu Pro Glu Leu Glu Glu Val Arg Tyr Leu Thr
20 25 30

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Val Glu Ser Gly Asp Gly Arg Gln Ser Thr Leu Tyr Glu Phe Gly Pro
        35                  40                  45

Lys Asp Ala Glu Lys Val Val Val Leu Pro Pro Tyr Gly Val Thr Phe
    50                  55                  60

Leu Leu Val Ala Arg Leu Ala Arg Leu Leu Ser Gln Arg Phe His Val
65                  70                  75                  80

Leu Ile Trp Glu Ser Arg Gly Cys Pro Asp Ser Ala Ile Pro Val Tyr
                85                  90                  95

Asp Thr Asp Leu Gly Leu Ala Asp Gln Ser Arg His Phe Ser Glu Val
            100                 105                 110

Leu Lys Gln Gln Gly Phe Glu Ala Phe His Phe Val Gly Trp Cys Gln
        115                 120                 125

Ala Ala Gln Leu Ala Val His Ala Thr Ala Ser Gly Gln Val Lys Pro
    130                 135                 140

Arg Thr Met Ser Trp Ile Ala Pro Ala Gly Leu Gly Tyr Ser Leu Val
145                 150                 155                 160

Lys Ser Glu Phe Asp Arg Cys Ala Leu Pro Ile Tyr Leu Glu Ile Glu
                165                 170                 175

Lys His Gly Leu Leu His Ala Glu Lys Leu Gly Arg Leu Leu Asn Lys
            180                 185                 190

Tyr Asn Gly Val Pro Ala Thr Ala Gln Asn Ala Ala Glu Lys Leu Thr
        195                 200                 205

Met Arg His Leu Ala Asp Pro Arg Met Thr Tyr Val Phe Ser Arg Tyr
    210                 215                 220

Met Lys Ala Tyr Glu Asp Asn Arg Leu Leu Ala Lys Gln Phe Val Ser
225                 230                 235                 240

Thr Ala Leu Asp Ser Val Pro Thr Leu Ala Ile His Cys Arg Asp Asp
                245                 250                 255

Thr Tyr Ser His Phe Ser Glu Ser Val Gln Leu Ser Lys Leu His Pro
            260                 265                 270

Ser Leu Glu Leu Arg Leu Leu Gly Lys Gly Gly His Leu Gln Ile Phe
        275                 280                 285

Asn Asp Pro Ala Thr Leu Ala Glu Tyr Val Leu Gly Phe Ile Asp Thr
    290                 295                 300

Arg Ala Ser Gln Ala Ala Ala Pro Ala Val Ala Gly Ala
305                 310                 315


<210> SEQ ID NO 42
<211> LENGTH: 459
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(459)
<223> OTHER INFORMATION: CysC

<400> SEQUENCE: 42

Met Ile Leu Pro Asn Asn Ile Gly Leu Asp Glu Arg Thr Gln Leu Ala
1               5                   10                  15

Arg Gln Ile Ser Ser Tyr Gln Lys Lys Phe His Val Trp Trp Arg Glu
            20                  25                  30

Arg Gly Pro Thr Glu Phe Leu Asp Arg Gln Met Arg Leu Arg Thr Pro
        35                  40                  45
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Thr Gly Ala Val Ser Gly Val Asp Trp Ala Glu Tyr Lys Thr Met Arg
    50                  55                  60

Pro Asp Glu Tyr Arg Trp Gly Leu Phe Met Val Pro Met Asp Gln Asp
65                  70                  75                  80

Glu Ile Ala Phe Gly Asp His Arg Gly Lys Lys Ala Trp Glu Glu Val
                85                  90                  95

Pro Ser Glu Tyr Arg Thr Leu Leu Leu Gln His Ile Cys Val Gln Ala
            100                 105                 110

Asp Val Glu Asn Ala Ala Val Glu Gln Ser Arg Leu Leu Thr Gln Met
        115                 120                 125

Ala Pro Ser Asn Pro Asp Leu Glu Asn Val Phe Gln Phe Phe Leu Glu
    130                 135                 140

Glu Gly Arg His Thr Trp Ala Met Val His Leu Leu Leu Ala His Phe
145                 150                 155                 160

Gly Glu Asp Gly Val Val Glu Ala Glu Ala Leu Leu Glu Arg Leu Ser
                165                 170                 175

Gly Asp Pro Arg Asn Pro Arg Leu Leu Glu Ala Phe Asn Tyr Pro Thr
            180                 185                 190

Glu Asp Trp Leu Ser His Phe Met Trp Cys Leu Leu Ala Asp Arg Val
        195                 200                 205

Gly Lys Tyr Gln Ile His Ala Val Thr Glu Ala Ser Phe Ala Pro Leu
    210                 215                 220

Ala Arg Ala Ala Lys Phe Met Met Phe Glu Glu Pro Leu His Ile Ala
225                 230                 235                 240

Met Gly Ala Val Gly Leu Glu Arg Val Leu Ala Arg Thr Ala Glu Val
                245                 250                 255

Thr Leu Arg Glu Gly Thr Phe Asp Thr Phe His Ala Gly Ala Ile Pro
            260                 265                 270

Phe Pro Val Val Gln Lys Tyr Leu Asn Tyr Trp Ala Pro Lys Val Tyr
        275                 280                 285

Asp Leu Phe Gly Asn Asp Gly Ser Glu Arg Ser Asn Glu Leu Phe Arg
    290                 295                 300

Ala Gly Leu Arg Arg Pro Arg Asn Phe Val Gly Ser Glu Ser Gln Ile
305                 310                 315                 320

Val Arg Ile Asp Glu Arg Met Gly Asp Gly Leu Thr Val Val Glu Val
                325                 330                 335

Glu Gly Glu Trp Ala Ile Asn Ala Ile Met Arg Arg Gln Phe Ile Ala
            340                 345                 350

Glu Val Gln Thr Leu Ile Asp Arg Trp Asn Ala Ser Leu Arg Ala Leu
        355                 360                 365

Gly Val Asp Phe Gln Leu Tyr Leu Pro His Glu Arg Phe Ser Arg Thr
    370                 375                 380

Tyr Gly Pro Cys Ala Gly Leu Pro Phe Asp Val Asp Gly Lys Leu Leu
385                 390                 395                 400

Pro Arg Gly Thr Glu Ala Lys Leu Ala Glu Tyr Phe Pro Thr Pro Arg
                405                 410                 415

Glu Leu Ala Asn Val Arg Ser Leu Met Gln Arg Glu Leu Ala Pro Gly
            420                 425                 430

Gln Tyr Ser Ser Trp Ile Ala Pro Ser Ala Thr Arg Leu Ser Ala Leu
        435                 440                 445

Val Gln Gly Arg Asn Thr Pro Lys Glu His Glu
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    450                 455


<210> SEQ ID NO 43
<211> LENGTH: 732
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(732)
<223> OTHER INFORMATION: CysD

<400> SEQUENCE: 43

Met Arg Cys Leu Ile Ile Asp Asn Tyr Asp Ser Phe Thr Trp Asn Leu
1               5                   10                  15

Ala Asp Tyr Val Ala Gln Thr Phe Gly Ser Glu Pro Leu Val Val Arg
            20                  25                  30

Asn Asp Gln His Thr Trp Gln Glu Ile Lys Ala Leu Gly Ser Phe Gly
        35                  40                  45

Cys Ile Leu Val Ser Pro Gly Pro Gly Ser Val Thr Asn Pro Lys Asp
    50                  55                  60

Phe Asn Val Ser Arg Asp Ala Leu Glu Gln Asp Glu Phe Pro Val Phe
65                  70                  75                  80

Gly Val Cys Leu Gly His Gln Gly Leu Ala Tyr Ile Tyr Gly Gly Glu
                85                  90                  95

Ile Thr His Ala Pro Val Pro Phe His Gly Arg Thr Ser Thr Ile Tyr
            100                 105                 110

His Asp Gly Thr Gly Val Phe Gln Gly Leu Pro Pro Ser Phe Asp Ala
        115                 120                 125

Val Arg Tyr His Ser Leu Val Val Arg Pro Glu Ser Leu Pro Ala Asn
    130                 135                 140

Leu Val Val Thr Ala Arg Thr Glu Cys Gly Leu Ile Met Gly Leu Arg
145                 150                 155                 160

His Val Ser Arg Pro Lys Trp Gly Val Gln Phe His Pro Glu Ser Ile
                165                 170                 175

Leu Thr Ala His Gly Leu Gln Leu Ile Ser Asn Phe Arg Asp Glu Ala
            180                 185                 190

Tyr Arg Tyr Ala Gly Lys Glu Val Pro Ser Arg Arg Pro His Ser Thr
        195                 200                 205

Ala Gly Asn Gly Val Gly Ala Gly Ala Ala Arg Arg Asp Pro Ser Ala
    210                 215                 220

Arg Arg Thr Pro Glu Arg Arg Arg Glu Leu Gln Thr Phe Thr Arg Arg
225                 230                 235                 240

Leu Ala Thr Ser Leu Glu Ala Glu Thr Val Phe Leu Gly Leu Tyr Ala
                245                 250                 255

Gly Arg Glu His Cys Phe Trp Leu Asp Ser Gln Ser Val Arg Glu Gly
            260                 265                 270

Ile Ser Arg Phe Ser Phe Met Gly Cys Val Pro Glu Gly Ser Leu Leu
        275                 280                 285

Thr Tyr Gly Ala Ala Glu Ala Ala Ser Glu Gly Gly Ala Glu Arg Tyr
    290                 295                 300

Leu Ala Ala Leu Glu Arg Ala Leu Glu Ser Arg Ile Val Val Arg Pro
305                 310                 315                 320

Val Asp Gly Leu Pro Phe Glu Phe His Gly Gly Tyr Ile Gly Phe Met
                325                 330                 335
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Thr Tyr Glu Met Lys Glu Ala Phe Gly Ala Ala Thr Thr His Lys Asn
            340                 345                 350

Thr Ile Pro Asp Ala Leu Trp Met His Val Lys Arg Phe Leu Ala Phe
        355                 360                 365

Asp His Ser Thr Arg Glu Val Trp Leu Val Ala Ile Ala Glu Leu Glu
    370                 375                 380

Glu Ser Ala Ser Val Leu Ala Trp Met Asp Glu Thr Ala Asp Ala Leu
385                 390                 395                 400

Lys Ser Leu Pro Arg Gly Thr Arg Ser Pro Gln Ser Leu Gly Leu Lys
                405                 410                 415

Ser Ile Ser Val Ser Met Asp Cys Gly Arg Asp Asp Tyr Phe Ala Ala
            420                 425                 430

Ile Glu Arg Cys Lys Glu Lys Ile Val Asp Gly Glu Ser Tyr Glu Val
        435                 440                 445

Cys Leu Thr Asn Gly Phe Ser Phe Asp Leu Lys Leu Asp Pro Val Glu
    450                 455                 460

Leu Tyr Val Thr Met Arg Arg Gly Asn Pro Ala Pro Phe Gly Ala Phe
465                 470                 475                 480

Ile Lys Thr Gly Lys Thr Cys Val Leu Ser Thr Ser Pro Glu Arg Phe
                485                 490                 495

Leu Lys Val Asp Glu Asp Gly Thr Val Gln Ala Lys Pro Ile Lys Gly
            500                 505                 510

Thr Cys Ala Arg Ser Asp Asp Pro Ala Thr Asp Ser Thr Asn Ala Ala
        515                 520                 525

Arg Leu Ala Ala Ser Glu Lys Asp Arg Ala Glu Asn Leu Met Ile Val
    530                 535                 540

Asp Leu Met Arg Asn Asp Leu Gly Arg Val Ser Val Pro Gly Ser Val
545                 550                 555                 560

His Val Ser Asn Leu Met Asp Ile Glu Ser Phe Lys Thr Val His Gln
                565                 570                 575

Met Val Ser Thr Val Glu Ser Thr Leu Thr Pro Glu Cys Ser Leu Val
            580                 585                 590

Asp Leu Leu Arg Ala Val Phe Pro Gly Gly Ser Ile Thr Gly Ala Pro
        595                 600                 605

Lys Ile Arg Thr Met Glu Ile Ile Asp Arg Leu Glu Lys Ser Pro Arg
    610                 615                 620

Gly Ile Tyr Cys Gly Thr Ile Gly Tyr Leu Gly Tyr Asn Arg Ile Ala
625                 630                 635                 640

Asp Leu Asn Ile Ala Ile Arg Thr Leu Ser Tyr Asp Gly Thr Leu Val
                645                 650                 655

Lys Phe Gly Ala Gly Gly Ala Ile Thr Tyr Leu Ser Gln Pro Glu Gly
            660                 665                 670

Glu Phe Gln Glu Ile Leu Leu Lys Ala Glu Ser Ile Leu Arg Pro Ile
        675                 680                 685

Trp Gln Tyr Ile Asn Gly Ala Gly Ala Pro Phe Glu Pro Gln Leu Arg
    690                 695                 700

Asp Arg Val Leu Cys Leu Glu Glu Lys Pro Arg Arg Val Ile Arg Gly
705                 710                 715                 720

His Gly Ser Ala Ile Asp Ala Val Glu Pro Ser Ala
                725                 730
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<210> SEQ ID NO 44
<211> LENGTH: 243
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(243)
<223> OTHER INFORMATION: CysE

<400> SEQUENCE: 44

Met Ile Ala Phe Asn Pro Gln Ala Arg Pro Arg Leu Arg Leu Phe Cys
1 5 10 15

Phe Pro Tyr Ala Gly Gly Asp Ala Asn Ile Phe Arg Asp Trp Ala Ala
20 25 30

Ala Met Pro Glu Gly Val Glu Val Leu Gly Val Gln Tyr Pro Gly Arg
35 40 45

Gly Thr Asn Leu Ala Leu Pro Pro Ile Ser Asp Cys Asp Glu Met Ala
50 55 60

Ser Gln Leu Leu Ala Val Met Thr Pro Leu Leu Gly Ile Asn Phe Ala
65 70 75 80

Phe Phe Gly His Ser Asn Gly Ala Leu Ile Ser Phe Glu Val Ala Arg
85 90 95

Arg Leu His Asp Glu Leu Lys Gly Arg Met Arg His His Phe Leu Ser
100 105 110

Ala Lys Ser Ala Pro His Tyr Pro Asn Asn Arg Ser Lys Ile Ser Gly
115 120 125

Leu Asn Asp Glu Asp Phe Leu Arg Ala Ile Arg Lys Met Gly Gly Thr
130 135 140

Pro Gln Glu Val Leu Asp Asp Ala Arg Leu Met Gln Ile Leu Leu Pro
145 150 155 160

Arg Leu Arg Ala Asp Phe Ala Leu Gly Glu Thr Tyr Val Phe Arg Pro
165 170 175

Gly Pro Thr Leu Thr Cys Asp Val Ser Ile Leu Arg Gly Glu Ser Asp
180 185 190

His Leu Val Asp Gly Glu Phe Val Gln Arg Trp Ser Glu Leu Thr Thr
195 200 205

Gly Gly Ala Ser Gln Tyr Ala Ile Asp Gly Gly His Phe Phe Leu Asn
210 215 220

Ser His Lys Ser Gln Val Val Ala Leu Val Arg Ala Ala Leu Leu Glu
225 230 235 240

Cys Val Leu

<210> SEQ ID NO 45
<211> LENGTH: 345
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(345)
<223> OTHER INFORMATION: CysF

<400> SEQUENCE: 45

Met Thr Ala Gln Asn Gln Ala Ser Ala Phe Ser Phe Asp Leu Phe Tyr
1 5 10 15

Thr Thr Val Asn Ala Tyr Tyr Arg Thr Ala Ala Val Lys Ala Ala Ile
20 25 30

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Glu Leu Gly Val Phe Asp Val Val Gly Glu Lys Gly Lys Thr Leu Ala
        35                  40                  45

Glu Ile Ala Lys Ala Cys Asn Ala Ser Pro Arg Gly Ile Arg Ile Leu
    50                  55                  60

Cys Arg Phe Leu Val Ser Ile Gly Phe Leu Lys Asn Ala Gly Glu Leu
65                  70                  75                  80

Phe Phe Leu Thr Arg Glu Met Ala Leu Phe Leu Asp Lys Lys Ser Pro
                85                  90                  95

Gly Tyr Leu Gly Gly Ser Ile Asp Phe Leu Leu Ser Pro Tyr Ile Met
            100                 105                 110

Asp Gly Phe Lys Asp Leu Ala Ser Val Val Arg Thr Gly Glu Leu Thr
        115                 120                 125

Leu Pro Glu Lys Gly Val Val Ala Pro Asp His Pro Gln Trp Val Thr
    130                 135                 140

Phe Ala Arg Ala Met Ala Pro Met Met Ser Leu Pro Ser Leu Leu Leu
145                 150                 155                 160

Ala Glu Leu Ala Asp Arg Gln Ala Asn Gln Pro Leu Lys Val Leu Asp
                165                 170                 175

Val Ala Ala Gly His Gly Leu Phe Gly Leu Ala Ile Ala Gln Arg Asn
            180                 185                 190

Pro Lys Ala His Val Thr Phe Leu Asp Trp Glu Asn Val Leu Gln Val
        195                 200                 205

Ala Arg Glu Asn Ala Thr Lys Ala Gly Val Leu Asp Arg Val Glu Phe
    210                 215                 220

Arg Pro Gly Asp Ala Phe Ser Val Asp Phe Gly Lys Glu Leu Asp Val
225                 230                 235                 240

Ile Leu Leu Thr Asn Phe Leu His His Phe Asp Glu Ala Gly Cys Glu
                245                 250                 255

Lys Ile Leu Lys Lys Ala His Ala Ala Leu Lys Glu Gly Gly Arg Val
            260                 265                 270

Leu Thr Phe Glu Phe Ile Ala Asn Glu Asp Arg Thr Ser Pro Pro Leu
        275                 280                 285

Ala Ala Thr Phe Ser Met Met Met Leu Gly Thr Thr Pro Gly Gly Glu
    290                 295                 300

Thr Tyr Ala Tyr Ser Asp Leu Glu Arg Met Phe Lys Asn Thr Gly Tyr
305                 310                 315                 320

Asp Gln Val Glu Leu Lys Ala Ile Pro Pro Ala Met Glu Lys Val Val
                325                 330                 335

Val Ser Ile Lys Gly Lys Ala Gln Leu
            340                 345


<210> SEQ ID NO 46
<211> LENGTH: 1992
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1992)
<223> OTHER INFORMATION: CysG

<400> SEQUENCE: 46

Met Ala Thr Lys Leu Ser Asp Phe Ala Leu Leu Asp Ser Glu Asp Ala
1               5                   10                  15
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Asn Val Ile Ser Arg Ser Asn Glu Thr Gly Ile Ser Leu Asp Leu Ser
            20                  25                  30

Lys Ser Val Val Asp Leu Phe Asn Leu Gln Val Glu Arg Ala Pro Asp
        35                  40                  45

Ala Thr Ala Cys Leu Gly Arg Gln Gly Arg Leu Thr Tyr Gly Glu Leu
    50                  55                  60

Asn Arg Arg Thr Asn Gln Leu Ala His His Leu Ile Ala Arg Gly Val
65                  70                  75                  80

Gly Pro Asp Val Pro Val Gly Val Leu Phe Glu Arg Ser Ala Glu Gln
                85                  90                  95

Leu Ile Ala Ile Leu Gly Val Leu Lys Ala Gly Gly Cys Tyr Val Pro
            100                 105                 110

Leu Asp Pro Gln Tyr Pro Ala Asp Tyr Met Gln Gln Val Leu Thr Asp
        115                 120                 125

Ala Arg Pro Arg Met Val Val Ser Ser Arg Ala Leu Gly Glu Arg Leu
    130                 135                 140

Arg Ser Gly Glu Glu Gln Ile Val Tyr Leu Asp Asp Glu Gln Leu Leu
145                 150                 155                 160

Ala Arg Glu Thr Arg Asp Pro Pro Val Lys Val Leu Pro Glu Gln Leu
                165                 170                 175

Ala Tyr Val Met Tyr Thr Ser Gly Ser Ser Gly Val Pro Lys Gly Val
            180                 185                 190

Met Val Pro His Arg Gln Ile Leu Asn Trp Leu His Ala Leu Leu Ala
        195                 200                 205

Arg Val Pro Phe Gly Glu Asn Glu Val Val Ala Gln Lys Thr Ser Thr
    210                 215                 220

Ser Phe Ala Ile Ser Val Lys Glu Leu Phe Ala Gly Leu Val Ala Gly
225                 230                 235                 240

Val Pro Gln Val Phe Ile Asp Asp Ala Thr Val Arg Asp Val Ala Ser
                245                 250                 255

Phe Val Arg Glu Leu Glu Gln Trp Arg Val Thr Arg Leu Tyr Thr Phe
            260                 265                 270

Pro Ser Gln Leu Ala Ala Ile Leu Ser Ser Val Asn Gly Ala Tyr Glu
        275                 280                 285

Arg Leu Arg Ser Leu Arg His Leu Tyr Ile Ser Ile Glu Pro Cys Pro
    290                 295                 300

Thr Glu Leu Leu Ala Lys Leu Arg Ala Ala Met Pro Trp Val Thr Pro
305                 310                 315                 320

Trp Tyr Ile Tyr Gly Cys Thr Glu Ile Asn Asp Val Thr Tyr Cys Asp
                325                 330                 335

Pro Gly Asp Gln Ala Gly Asn Thr Gly Phe Val Pro Ile Gly Arg Pro
            340                 345                 350

Ile Arg Asn Thr Arg Val Phe Val Leu Asp Glu Glu Leu Arg Met Val
        355                 360                 365

Pro Val Gly Ala Met Gly Glu Met Tyr Val Glu Ser Leu Ser Thr Ala
    370                 375                 380

Arg Gly Tyr Trp Gly Leu Pro Glu Leu Thr Ala Glu Arg Phe Ile Ala
385                 390                 395                 400

Asn Pro His Ala Glu Asp Gly Ser Arg Leu Tyr Lys Thr Gly Asp Leu
                405                 410                 415

Ala Arg Tyr Leu Pro Asp Gly Ser Leu Glu Phe Leu Gly Arg Arg Asp
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            420                 425                 430

Tyr Glu Val Lys Ile Arg Gly Tyr Arg Val Asp Val Arg Gln Val Glu
        435                 440                 445

Lys Val Leu Gly Ala His Pro Asp Ile Leu Glu Val Ala Val Val Gly
    450                 455                 460

Trp Pro Leu Gly Gly Ala Asn Pro Gln Leu Val Ala Tyr Val Val Pro
465                 470                 475                 480

Arg Ala Lys Gly Ala Ala Pro Ile Gln Glu Ile Arg Asp Tyr Leu Ser
                485                 490                 495

Ala Ser Leu Pro Ala Tyr Met Val Pro Thr Ile Phe Gln Val Leu Ala
            500                 505                 510

Ala Leu Pro Arg Leu Pro Asn Asp Lys Val Asp Arg Leu Ser Leu Pro
        515                 520                 525

Asp Pro Lys Val Glu Glu Gln Thr Glu Gly Tyr Val Ala Pro Arg Thr
    530                 535                 540

Glu Thr Glu Lys Val Leu Ala Glu Ile Trp Ser Asp Val Leu Ser Gln
545                 550                 555                 560

Gly Arg Ala Pro Leu Thr Val Gly Ala Thr His Asn Phe Phe Glu Leu
                565                 570                 575

Gly Gly His Ser Leu Leu Ala Ala Gln Met Phe Ser Arg Ile Arg Gln
            580                 585                 590

Lys Phe Asp Leu Glu Leu Pro Ile Asn Thr Leu Phe Glu Thr Pro Val
        595                 600                 605

Leu Glu Gly Phe Ala Ser Ala Val Asp Ala Ala Leu Ala Glu Arg Asn
    610                 615                 620

Gly Pro Ala Gln Arg Leu Ile Ser Met Thr Asp Arg Gly Gln Ala Leu
625                 630                 635                 640

Pro Leu Ser His Val Gln Glu Arg Leu Trp Phe Val His Glu His Met
                645                 650                 655

Val Glu Gln Arg Ser Ser Tyr Asn Val Ala Phe Ala Cys His Met Arg
            660                 665                 670

Gly Lys Gly Leu Ser Met Pro Ala Leu Arg Ala Ala Ile Asn Gly Leu
        675                 680                 685

Val Ala Arg His Glu Thr Leu Arg Thr Thr Phe Val Val Ser Glu Gly
    690                 695                 700

Gly Gly Asp Pro Val Gln Arg Ile Ala Asp Ser Leu Trp Ile Glu Val
705                 710                 715                 720

Pro Leu Tyr Glu Val Asp Ala Ser Glu Val Pro Ala Arg Met Ala Ala
                725                 730                 735

His Ala Gly His Val Phe Asp Leu Ala Lys Gly Pro Leu Leu Lys Thr
            740                 745                 750

Ser Val Leu Arg Val Thr Pro Asp His His Val Phe Leu Met Asn Met
        755                 760                 765

His His Ile Ile Cys Asp Gly Trp Ser Ile Asp Ile Leu Leu Arg Asp
    770                 775                 780

Leu Tyr Glu Phe Tyr Lys Ala Ala Glu Thr Gly Ser Gln Pro Asn Leu
785                 790                 795                 800

Pro Val Leu Pro Ile Gln Tyr Ala Asp Tyr Ser Val Trp Gln Arg Gln
                805                 810                 815

Gln Asp Leu Ser Ser His Leu Asp Tyr Trp Lys Lys Thr Leu Glu Gly
            820                 825                 830
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Tyr Gln Glu Gly Leu Ser Leu Pro Tyr Asp Phe Ala Arg Pro Ser Asn
        835                 840                 845

Arg Thr Trp Arg Ala Ala Ser Val Arg His Gln Tyr Pro Ala Glu Leu
    850                 855                 860

Ala Thr Arg Leu Ser Glu Val Ser Lys Ser His Gln Ala Thr Val Phe
865                 870                 875                 880

Met Thr Leu Met Ala Ser Thr Ala Ile Val Leu Asn Arg Tyr Thr Gly
                885                 890                 895

Arg Asp Asp Leu Cys Val Gly Ala Thr Val Ala Gly Arg Asp His Phe
            900                 905                 910

Glu Leu Glu Asn Leu Ile Gly Phe Phe Val Asn Ile Leu Ala Ile Arg
        915                 920                 925

Leu Asp Leu Ser Gly Asn Pro Thr Ala Glu Thr Val Leu Gln Arg Ala
    930                 935                 940

Arg Ala Gln Val Leu Glu Gly Met Lys His Arg Asp Leu Pro Phe Glu
945                 950                 955                 960

His Ile Leu Ala Ala Leu Gln Lys Gln Arg Asp Ser Ser Gln Ile Pro
                965                 970                 975

Leu Val Pro Val Met Val Arg His Gln Asn Phe Pro Thr Val Thr Ser
            980                 985                 990

Gln Glu Gln Gly Leu Asp Leu Gly  Ile Gly Glu Ile Glu  Phe Gly Glu
        995                 1000                1005

Arg Thr  Thr Pro Asn Glu Leu  Asp Ile Gln Phe Ile  Gly Glu Gly
    1010                1015                1020

Ser Thr  Leu Glu Val Val Val  Glu Tyr Ala Lys Asp  Leu Phe Ser
    1025                1030                1035

Glu Arg  Thr Ile Gln Arg Leu  Ile Thr His Leu Gln  Gln Val Leu
    1040                1045                1050

Gln Thr  Leu Val Asp Lys Pro  Asp Cys Arg Leu Thr  Asp Phe Pro
    1055                1060                1065

Leu Val  Ala Gly Asp Ala Leu  Gln Gly Gly Val Ser  Gly Ser Gly
    1070                1075                1080

Gly Ala  Thr Lys Thr Gly Lys  Leu Asp Val Ser Lys  Ser Pro Val
    1085                1090                1095

Glu Leu  Phe Asn Glu Arg Val  Glu Ala Ser Pro Asp  Ala Val Ala
    1100                1105                1110

Cys Met  Gly Ala Asp Gly Ser  Leu Thr Tyr Arg Glu  Leu Asp Arg
    1115                1120                1125

Arg Ala  Asn Gln Val Ala Arg  His Leu Met Gly Arg  Gly Val Gly
    1130                1135                1140

Arg Glu  Thr Arg Val Gly Leu  Trp Phe Glu Arg Ser  Pro Asp Leu
    1145                1150                1155

Leu Val  Ala Leu Leu Gly Ile  Leu Lys Ala Gly Gly  Cys Phe Val
    1160                1165                1170

Pro Leu  Asp Pro Ser Tyr Pro  Gln Glu Tyr Ile Asn  Asn Ile Val
    1175                1180                1185

Ala Asp  Ala Gln Pro Leu Leu  Val Met Ser Ser Arg  Ala Leu Gly
    1190                1195                1200

Ser Arg  Leu Ser Leu Glu Ala  Gly Arg Leu Val Tyr  Leu Asp Asp
    1205                1210                1215
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Ala Leu  Ala Ala Ser Thr Asp  Ala Ser Asp Pro Gln  Val Arg Ile
    1220                 1225                 1230

Asp Pro  Glu Gln Leu Ile Tyr  Val Met Tyr Thr Ser  Gly Ser Thr
    1235                 1240                 1245

Gly Leu  Pro Lys Gly Val Leu  Val Pro His Arg Gln  Ile Leu Asn
    1250                 1255                 1260

Trp Leu  Tyr Pro Leu Trp Ala  Met Val Pro Phe Gly  Gln Asp Glu
    1265                 1270                 1275

Val Val  Ala Gln Lys Thr Ser  Thr Ala Phe Ala Val  Ser Met Lys
    1280                 1285                 1290

Glu Leu  Phe Thr Gly Leu Leu  Ala Gly Val Pro Gln  Val Phe Ile
    1295                 1300                 1305

Asp Gly  Thr Val Val Lys Asp  Ala Ala Ala Phe Val  Leu His Leu
    1310                 1315                 1320

Glu Arg  Trp Arg Val Thr Arg  Leu Tyr Thr Leu Pro  Ser His Leu
    1325                 1330                 1335

Asp Ala  Ile Leu Ser His Val  Asp Gly Ala Ala Glu  Arg Leu Arg
    1340                 1345                 1350

Ser Leu  Arg His Val Ile Leu  Ala Gly Glu Pro Cys  Pro Val Glu
    1355                 1360                 1365

Leu Met  Glu Lys Leu Arg Glu  Thr Leu Pro Ser Cys  Thr Ala Trp
    1370                 1375                 1380

Phe Asn  Tyr Gly Cys Thr Glu  Val Asn Asp Ile Ser  Tyr Cys Val
    1385                 1390                 1395

Pro Asn  Glu Gln Phe His Ser  Ser Gly Phe Val Pro  Ile Gly Arg
    1400                 1405                 1410

Pro Ile  Gln Tyr Thr Arg Ala  Leu Val Leu Asp Asp  Glu Leu Arg
    1415                 1420                 1425

Thr Val  Pro Val Gly Ile Met  Gly Glu Ile Tyr Val  Glu Ser Pro
    1430                 1435                 1440

Gly Thr  Ala Arg Gly Tyr Trp  Arg Gln Pro Asp Leu  Thr Ala Glu
    1445                 1450                 1455

Arg Phe  Ile Pro Asn Pro Phe  Gly Glu Pro Gly Ser  Arg Leu Tyr
    1460                 1465                 1470

Arg Thr  Gly Asp Met Ala Arg  Cys Leu Glu Asp Gly  Ser Leu Glu
    1475                 1480                 1485

Phe Leu  Gly Arg Arg Asp Tyr  Glu Val Lys Ile Arg  Gly His Arg
    1490                 1495                 1500

Val Asp  Val Arg Gln Val Glu  Lys Ile Leu Ala Ser  His Pro Glu
    1505                 1510                 1515

Val Leu  Glu Ser Ala Val Leu  Gly Trp Pro Arg Gly  Ala Lys Asn
    1520                 1525                 1530

Pro Gln  Leu Leu Ala Tyr Ala  Ala Thr Lys Pro Gly  Arg Pro Leu
    1535                 1540                 1545

Ser Thr  Glu Asn Val Arg Glu  Tyr Leu Ser Ala Arg  Leu Pro Thr
    1550                 1555                 1560

Tyr Met  Val Pro Thr Leu Tyr  Gln Phe Leu Pro Ala  Leu Pro Arg
    1565                 1570                 1575

Leu Pro  Asn Gly Lys Leu Asp  Arg Phe Gly Leu Pro  Asp His Lys
    1580                 1585                 1590

Lys Val  Glu Val Gly Gly Val  Tyr Val Ala Pro Gln  Thr Pro Thr
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    1595                1600                1605

Glu Lys  Val Leu Ala Gly Leu  Trp Ala Glu Cys Leu  Lys Gln Gly
    1610                1615                1620

Asp Met  Pro Ala Pro Gln Val  Gly Arg Leu His Asn  Phe Phe Asp
    1625                1630                1635

Leu Gly  Gly His Ser Leu Leu  Ala Asn Arg Val Leu  Met Gln Val
    1640                1645                1650

Gln Arg  His Phe Gly Val Ser  Leu Gly Ile Ser Ala  Leu Phe Gly
    1655                1660                1665

Ser Pro  Val Leu Asn Asp Phe  Ala Ala Ala Ile Asp  Lys Ala Leu
    1670                1675                1680

Gly Thr  Glu Glu Pro Gly Glu  Glu Gly Ser Ser Asp  Ala Arg Glu
    1685                1690                1695

Val Ala  Ala Lys Asp Thr Ser  Val Leu Val Pro Leu  Ser Thr His
    1700                1705                1710

Gly Thr  Leu Pro Ser Leu Phe  Cys Val His Pro Val  Gly Gly Gln
    1715                1720                1725

Val His  Ala Tyr Arg Glu Leu  Ala Gln Ala Met Glu  Lys His Ala
    1730                1735                1740

Ser Met  Tyr Ala Leu Gln Ser  Glu Gly Ala Arg Glu  Phe Asp Thr
    1745                1750                1755

Ile Glu  Thr Leu Ala Arg Phe  Tyr Ala Asp Ala Ile  Arg Gly Ala
    1760                1765                1770

Gln Pro  Asp Gly Ser Tyr Arg  Leu Leu Gly Trp Ser  Ser Gly Gly
    1775                1780                1785

Leu Ile  Thr Leu Ala Ile Ala  Arg Glu Leu Glu His  Gln Gly Cys
    1790                1795                1800

Ala Val  Glu Tyr Val Gly Leu  Val Asp Ser Lys Pro  Ile Pro Arg
    1805                1810                1815

Leu Ala  Gly Glu Arg Gly Trp  Ala Ser Leu Ile Ala  Ala Thr Asn
    1820                1825                1830

Ile Leu  Gly Ala Met Arg Gly  Arg Gly Phe Ser Val  Ala Glu Val
    1835                1840                1845

Asp Ala  Ala Gly Lys Ile Leu  Glu Ser Arg Gly Trp  Thr Glu Glu
    1850                1855                1860

Ser Phe  Asp Ser Glu Gly His  Ala Ala Leu Glu Glu  Leu Ala Arg
    1865                1870                1875

His Phe  Gly Ile Thr Val Ala  Gln Glu Ser Ser Glu  Tyr Leu Leu
    1880                1885                1890

Ala Arg  Phe Lys Thr Thr Lys  Tyr Tyr Leu Ser Leu  Phe Ala Gly
    1895                1900                1905

Phe Lys  Pro Ala Ala Leu Gly  Pro Glu Thr Tyr Leu  Tyr Glu Ala
    1910                1915                1920

Ser Glu  Arg Val Gly Ala Thr  Ser Asn Asp Asp Thr  Gly Glu Trp
    1925                1930                1935

Gly Asp  Ala Leu Asp Arg Lys  Ala Leu Arg Ala Asn  Ile Val Gln
    1940                1945                1950

Val Pro  Gly Asn His Tyr Thr  Val Leu Gln Gly Glu  Asn Val Leu
    1955                1960                1965

Gln Leu  Ala Gly Arg Ile Ala  Glu Ala Leu Ser Ala  Ile Asp Asn
    1970                1975                1980
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Ser Val  Val Thr Arg Thr Arg  Ala Ser
    1985                1990


<210> SEQ ID NO 47
<211> LENGTH: 975
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(975)
<223> OTHER INFORMATION: CysH

<400> SEQUENCE: 47

Met Asp Asn Arg Glu Ile Ala Pro Thr Gln Ser Ala Arg Thr Arg Asp
1               5                   10                  15

Ala Tyr Thr Ala Val Pro Pro Ala Lys Ala Glu Tyr Pro Ser Asp Val
            20                  25                  30

Cys Val His Gln Leu Phe Glu Leu Gln Ala Asp Arg Ile Pro Asp Ala
        35                  40                  45

Val Ala Ala Arg Ala Gly Asn Glu Ser Leu Thr Tyr Arg Glu Leu Asn
    50                  55                  60

Phe Arg Ala Asn Gln Leu Ala Arg Tyr Leu Val Ala Lys Gly Val Val
65                  70                  75                  80

Pro Arg Gly Ser Val Ala Val Leu Met Asn Arg Thr Pro Ala Cys Leu
                85                  90                  95

Val Ser Leu Leu Ala Ile Ile Lys Ala Gly Ala Ala Tyr Val Pro Val
            100                 105                 110

Asp Ala Gly Leu Pro Ala Lys Arg Val Asp Tyr Ile Leu Thr Asp Ser
        115                 120                 125

Gly Ala Thr Cys Val Leu Thr Asp Arg Glu Thr Arg Ser Leu Leu Asp
    130                 135                 140

Glu Pro Arg Ser Ala Ser Thr Leu Val Ile Asp Val Asp Asp Pro Ser
145                 150                 155                 160

Ile Tyr Ser Gly Glu Thr Ser Asn Leu Gly Leu Ala Val Asp Pro Glu
                165                 170                 175

Gln Gln Val Tyr Cys Ile Tyr Thr Ser Gly Ser Thr Gly Leu Pro Lys
            180                 185                 190

Gly Val Met Val Gln His Arg Ala Leu Met Asn Tyr Val Trp Trp Ala
        195                 200                 205

Lys Lys Gln Tyr Val Thr Asp Ala Val Glu Ser Phe Ala Leu Tyr Ser
    210                 215                 220

Ser Leu Ser Phe Asp Leu Thr Val Thr Ser Ile Phe Val Pro Leu Ile
225                 230                 235                 240

Ser Gly Arg Cys Ile Asp Val Tyr Pro Asp Leu Gly Glu Asp Val Pro
                245                 250                 255

Val Ile Asn Arg Val Leu Glu Asp Asn Lys Val Asp Val Val Lys Leu
            260                 265                 270

Thr Pro Ala His Leu Ala Leu Leu Arg Asn Thr Asp Leu Ser Gln Ser
        275                 280                 285

Arg Leu Lys Val Leu Ile Leu Gly Gly Glu Asp Leu Arg Ala Glu Thr
    290                 295                 300

Ala Gly Asp Val His Lys Arg Leu Asp Gly Arg Ala Val Ile Tyr Asn
305                 310                 315                 320
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Glu Tyr Gly Pro Thr Glu Thr Val Val Gly Cys Met Ile His Arg Tyr
                325                 330                 335

Asp Pro Ala Val Asp Leu His Gly Ser Val Pro Ile Gly Val Gly Ile
            340                 345                 350

Asp Asn Met Arg Ile Tyr Leu Leu Asp Asp Arg Arg Arg Pro Val Lys
        355                 360                 365

Pro Gly Glu Val Gly Glu Ile Tyr Ile Gly Gly Asp Gly Val Thr Leu
    370                 375                 380

Gly Tyr Lys Asp Lys Pro Gln Val Thr Ala Asp His Phe Ile Ser Asn
385                 390                 395                 400

Pro Phe Val Glu Gly Glu Arg Leu Tyr Ala Ser Gly Asp Leu Gly Arg
                405                 410                 415

Val Asn Glu Arg Gly Ala Leu Val Phe Leu Gly Arg Lys Asp Leu Gln
            420                 425                 430

Ile Lys Leu Arg Gly Tyr Arg Ile Glu Leu Gly Glu Ile Glu Ser Ala
        435                 440                 445

Leu Leu Ser Tyr Pro Gly Ile Lys Glu Cys Ile Val Asp Ser Thr Lys
    450                 455                 460

Thr Ala Gln Ser Gln Ala Ala Ala Gln Leu Thr Tyr Cys Thr Lys Cys
465                 470                 475                 480

Gly Leu Ala Ser Ser Phe Pro Asn Thr Thr Tyr Ser Ala Glu Gly Val
                485                 490                 495

Cys Asn His Cys Glu Ala Phe Asp Lys Tyr Arg Ser Val Val Asp Asp
            500                 505                 510

Tyr Phe Ser Thr Met Asp Glu Leu Gln Ser Ile Val Thr Glu Met Lys
        515                 520                 525

Ser Ile His Asn Ser Lys Tyr Asp Cys Ile Val Ala Leu Ser Gly Gly
    530                 535                 540

Lys Asp Ser Thr Tyr Ala Leu Cys Arg Met Ile Glu Thr Gly Ala Arg
545                 550                 555                 560

Val Leu Ala Phe Thr Leu Asp Asn Gly Tyr Ile Ser Glu Glu Ala Lys
                565                 570                 575

Gln Asn Ile Asn Arg Val Val Ala Arg Leu Gly Val Asp His Arg Tyr
            580                 585                 590

Leu Ser Thr Gly His Met Lys Glu Ile Phe Val Asp Ser Leu Lys Arg
        595                 600                 605

His Ser Asn Val Cys Asn Gly Cys Phe Lys Thr Ile Tyr Thr Phe Ala
    610                 615                 620

Ile Asn Leu Ala Gln Glu Val Gly Val Lys His Val Val Met Gly Leu
625                 630                 635                 640

Ser Lys Gly Gln Leu Phe Glu Thr Arg Leu Ser Ala Leu Phe Arg Thr
                645                 650                 655

Ser Thr Phe Asp Asn Ala Ala Phe Glu Lys Ser Leu Val Asp Ala Arg
            660                 665                 670

Lys Ile Tyr His Arg Ile Asp Asp Ala Val Ser Arg Leu Leu Asp Thr
        675                 680                 685

Thr Cys Val Lys Asn Asp Lys Val Ile Glu Asn Ile Arg Phe Val Asp
    690                 695                 700

Phe Tyr Arg Tyr Cys His Ala Ser Arg Gln Glu Met Tyr Asp Tyr Ile
705                 710                 715                 720

Gln Glu Arg Val Gly Trp Ala Arg Pro Ile Asp Thr Gly Arg Ser Thr
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               725                 730                 735

Asn Cys Leu Leu Asn Asp Val Gly Ile Tyr Val His Asn Lys Glu Arg
            740                 745                 750

Arg Tyr His Asn Tyr Ser Leu Pro Tyr Ser Trp Asp Val Arg Met Gly
        755                 760                 765

His Ile Ser Arg Glu Glu Ala Met Arg Glu Leu Asp Asp Ser Ala Asp
    770                 775                 780

Ile Asp Val Glu Arg Val Glu Gly Ile Ile Lys Asp Leu Gly Tyr Glu
785                 790                 795                 800

Leu Asn Asp Gln Val Val Gly Ser Ala Glu Ala Gln Leu Val Ala Tyr
                805                 810                 815

Tyr Val Ser Ala Glu Glu Phe Pro Ala Ser Asp Leu Arg Gln Phe Leu
            820                 825                 830

Ser Glu Ile Leu Pro Glu Tyr Met Val Pro Arg Ser Phe Val Gln Leu
        835                 840                 845

Asp Ser Ile Pro Leu Thr Pro Asn Gly Lys Val Asn Arg Gln Ala Leu
    850                 855                 860

Pro Lys Pro Asp Leu Leu Arg Lys Ala Gly Thr Asp Gly Gln Ala Ala
865                 870                 875                 880

Pro Arg Thr Pro Val Glu Lys Gln Leu Ala Glu Leu Trp Lys Glu Val
                885                 890                 895

Leu Gln Val Asp Ser Val Gly Ile His Asp Asn Phe Phe Glu Met Gly
            900                 905                 910

Gly His Ser Leu Pro Ala Leu Met Leu Leu Tyr Lys Ile Asp Ser Gln
        915                 920                 925

Phe His Lys Thr Ile Ser Ile Gln Glu Phe Ser Lys Val Pro Thr Ile
    930                 935                 940

Ser Ala Leu Ala Ala His Leu Gly Ser Asp Thr Glu Ala Val Pro Pro
945                 950                 955                 960

Gly Leu Gly Glu Val Val Asp Gln Ser Ala Pro Ala Tyr Arg Gly
                965                 970                 975


<210> SEQ ID NO 48
<211> LENGTH: 272
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(272)
<223> OTHER INFORMATION: CysI

<400> SEQUENCE: 48

Val Arg Phe Val Thr Val Asn Gly Glu Asp Ser Ala Val Cys Ser Val
1               5                   10                  15

Leu Asp Arg Gly Leu Gln Phe Gly Asp Gly Leu Phe Glu Thr Met Leu
            20                  25                  30

Cys Val Gly Gly Ala Pro Val Asp Phe Pro Glu His Trp Ala Arg Leu
        35                  40                  45

Asp Glu Gly Cys Arg Arg Leu Gly Ile Glu Cys Pro Asp Ile Arg Arg
    50                  55                  60

Glu Val Thr Ala Ala Ile Ala Arg Trp Gly Ala Pro Arg Ala Val Ala
65                  70                  75                  80

Lys Leu Val Val Thr Arg Gly Ser Thr Glu Arg Gly Tyr Arg Cys Ala
                85                  90                  95
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Pro Ser Val Arg Pro Asn Trp Ile Leu Thr Ile Thr Asp Ala Pro Lys
            100                 105                 110

Tyr Pro Leu Ala His Glu Asp Arg Gly Val Ala Val Lys Leu Cys Arg
        115                 120                 125

Thr Leu Val Ser Leu Asp Asp Pro Gln Leu Ala Gly Leu Lys His Leu
    130                 135                 140

Asn Arg Leu Pro Gln Val Leu Ala Arg Arg Glu Trp Asp Asp Glu Tyr
145                 150                 155                 160

His Asp Gly Leu Leu Thr Asp His Gly Gly His Leu Val Glu Gly Cys
                165                 170                 175

Thr Ser Asn Leu Phe Leu Val Ala Asp Gly Ala Leu Arg Thr Pro Asp
            180                 185                 190

Leu Thr Ala Cys Gly Val Arg Gly Ile Val Arg Gln Lys Val Leu Asp
        195                 200                 205

His Ser Lys Ala Ile Gly Ile Arg Cys Glu Val Thr Thr Leu Lys Leu
    210                 215                 220

Arg Asp Leu Glu His Ala Asp Glu Val Phe Leu Thr Asn Ser Val Tyr
225                 230                 235                 240

Gly Ile Val Pro Val Gly Ser Val Asp Gly Met Arg Tyr Arg Ile Gly
                245                 250                 255

Pro Thr Thr Ala Arg Leu Leu Lys Asp Leu Cys Gln Gly Val Tyr Phe
            260                 265                 270


<210> SEQ ID NO 49
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(327)
<223> OTHER INFORMATION: CysJ

<400> SEQUENCE: 49

Met Thr Gly Asn Leu Asp Ser Ala Ala Trp Pro Val Ile Ile Thr Pro
1               5                   10                  15

Gly Gln Gln Pro Ala Ala Leu Glu Asp Trp Val Ser Ala Asn Arg Asp
            20                  25                  30

Gly Leu Glu Arg Gln Leu Thr Glu Cys Lys Ala Ile Leu Phe Arg Gly
        35                  40                  45

Phe Arg Ser Arg Asn Gly Phe Glu Ser Ile Ala Asn Ser Phe Phe Asp
    50                  55                  60

Arg Arg Leu Asn Tyr Thr Tyr Arg Ser Thr Pro Arg Thr Asp Leu Gly
65                  70                  75                  80

Gln Asn Leu Tyr Thr Ala Thr Glu Tyr Pro Lys Gln Leu Ser Ile Pro
                85                  90                  95

Gln His Cys Glu Asn Ala Tyr Gln Arg Asp Trp Pro Met Lys Leu Leu
            100                 105                 110

Phe His Cys Val Glu Pro Ala Ser Lys Gly Gly Arg Thr Pro Leu Ala
        115                 120                 125

Asp Met Thr Lys Val Thr Ala Met Ile Pro Ala Glu Ile Lys Glu Glu
    130                 135                 140

Phe Ala Arg Lys Lys Val Gly Tyr Val Arg Asn Tyr Arg Ala Gly Val
145                 150                 155                 160
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Asp Leu Pro Trp Glu Glu Val Phe Gly Thr Ser Asn Lys Ala Glu Val
                165                 170                 175

Glu Lys Phe Cys Val Glu Asn Gly Ile Glu Tyr His Trp Thr Glu Gly
            180                 185                 190

Gly Leu Lys Thr Ile Gln Val Cys Gln Ala Phe Ala Ser His Pro Leu
        195                 200                 205

Thr Gly Glu Thr Ile Trp Phe Asn Gln Ala His Leu Phe His Leu Ser
    210                 215                 220

Ala Leu Asp Pro Ala Ser Gln Lys Met Met Leu Ser Phe Phe Gly Glu
225                 230                 235                 240

Gly Gly Leu Pro Arg Asn Ser Tyr Phe Gly Asp Gly Ser Ala Ile Gly
                245                 250                 255

Ser Asp Val Leu Asp Gln Ile Arg Ser Ala Tyr Glu Arg Asn Lys Val
            260                 265                 270

Ser Phe Glu Trp Gln Lys Asp Asp Val Leu Leu Ile Asp Asn Met Leu
        275                 280                 285

Val Ser His Gly Arg Asp Pro Phe Glu Gly Ser Arg Arg Val Leu Val
    290                 295                 300

Cys Met Ala Glu Pro Tyr Ser Glu Val Gln Arg Arg Gly Phe Ala Gly
305                 310                 315                 320

Ala Thr Asn Ser Gly Arg Ser
                325


<210> SEQ ID NO 50
<211> LENGTH: 4545
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4140)
<223> OTHER INFORMATION: CysK
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(4545)
<223> OTHER INFORMATION: CysK

<400> SEQUENCE: 50

Met Leu Leu Glu Gly Glu Leu Glu Gly Tyr Glu Asp Gly Leu Glu Leu
1               5                   10                  15

Pro Tyr Asp Phe Pro Arg Thr Ser Asn Arg Ala Trp Arg Ala Ala Thr
            20                  25                  30

Phe Gln His Ser Tyr Pro Pro Glu Leu Ala Arg Lys Val Ala Glu Leu
        35                  40                  45

Ser Arg Glu Gln Gln Ser Thr Leu Phe Met Ser Leu Val Ala Ser Leu
    50                  55                  60

Ala Val Val Leu Asn Arg Tyr Thr Gly Arg Glu Asp Val Cys Ile Gly
65                  70                  75                  80

Thr Thr Val Ala Gly Arg Ala Gln Val Gly Ala Leu Gly Asp Leu Ser
                85                  90                  95

Gly Ser Thr Val Asp Ile Leu Pro Leu Arg Leu Asp Leu Ser Gly Ala
            100                 105                 110

Pro Ser Leu His Glu Val Leu Arg Arg Thr Lys Ala Val Val Leu Glu
        115                 120                 125

Gly Phe Glu His Glu Ala Leu Pro Cys Gln Ile Pro Leu Val Pro Val
    130                 135                 140
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Val Val Arg His Gln Asn Phe Pro Met Ala Arg Leu Glu Gly Trp Ser
145                 150                 155                 160

Glu Gly Val Glu Leu Lys Lys Phe Glu Leu Ala Gly Glu Arg Thr Thr
                165                 170                 175

Ala Ser Glu Gln Asp Trp Gln Phe Phe Gly Asp Gly Ser Ser Leu Glu
            180                 185                 190

Leu Ser Leu Glu Tyr Ala Ala Glu Leu Phe Ser Glu Lys Thr Val Lys
        195                 200                 205

Arg Met Val Glu His His Gln Arg Val Leu Glu Ala Leu Val Glu Gly
    210                 215                 220

Leu Glu Glu Val Arg Leu His Glu Val Arg Leu Leu Thr Glu Glu Glu
225                 230                 235                 240

Glu Gly Leu His Gly Arg Leu Asn Asp Thr Ala Arg Glu Leu Glu Glu
                245                 250                 255

Arg Trp Ser Leu Ala Glu Thr Phe Glu Arg Gln Val Arg Glu Thr Pro
            260                 265                 270

Glu Ala Val Ala Cys Val Gly Val Glu Val Ala Thr Gly Gly His Ser
        275                 280                 285

Arg Pro Thr Tyr Arg Gln Leu Thr Tyr Arg Gln Leu Asn Ala Arg Ala
    290                 295                 300

Asn Gln Val Ala Arg Arg Leu Arg Ala Leu Gly Val Gly Ala Glu Thr
305                 310                 315                 320

Arg Val Ala Val Leu Ser Asp Arg Ser Pro Glu Leu Leu Val Ala Met
                325                 330                 335

Leu Ala Ile Phe Lys Ala Gly Gly Cys Tyr Val Pro Val Asp Pro Gln
            340                 345                 350

Tyr Pro Gly Ser Tyr Ile Glu Gln Ile Leu Glu Asp Ala Ala Pro Gln
        355                 360                 365

Val Val Leu Gly Lys Arg Gly Arg Ala Asp Gly Val Arg Val Asp Val
    370                 375                 380

Trp Leu Glu Leu Asp Gly Ala Gln Arg Leu Thr Asp Glu Ala Leu Ala
385                 390                 395                 400

Ala Gln Glu Glu Gly Glu Leu Glu Gly Ala Glu Arg Pro Glu Ser Gln
                405                 410                 415

Gln Leu Ala Cys Leu Met Tyr Thr Ser Gly Ser Thr Gly Arg Pro Lys
            420                 425                 430

Gly Val Met Val Pro Tyr Ser Gln Leu His Asn Trp Leu Glu Ala Gly
        435                 440                 445

Lys Glu Arg Ser Pro Leu Glu Arg Gly Glu Val Met Leu Gln Lys Thr
    450                 455                 460

Ala Ile Ala Phe Ala Val Ser Val Lys Glu Leu Leu Ser Gly Leu Leu
465                 470                 475                 480

Ala Gly Val Ala Gln Val Met Val Pro Glu Thr Leu Val Lys Asp Ser
                485                 490                 495

Val Ala Leu Ala Gln Glu Ile Glu Arg Trp Arg Val Thr Arg Ile His
            500                 505                 510

Leu Val Pro Ser His Leu Gly Ala Leu Leu Glu Gly Ala Gly Glu Glu
        515                 520                 525

Ala Lys Gly Leu Arg Ser Leu Lys Tyr Val Ile Thr Ala Gly Glu Ala
    530                 535                 540

Leu Ala Gln Gly Val Arg Glu Glu Ala Arg Arg Lys Leu Pro Gly Ala
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545                 550                 555                 560

Gln Leu Trp Asn Asn Tyr Gly Cys Thr Glu Leu Asn Asp Val Thr Tyr
                565                 570                 575

His Pro Ala Ser Glu Gly Gly Gly Asp Thr Val Phe Val Pro Ile Gly
            580                 585                 590

Arg Pro Ile Ala Asn Thr Arg Val Tyr Val Leu Asp Glu Gln Leu Arg
        595                 600                 605

Arg Val Pro Val Gly Val Met Gly Glu Leu Tyr Val Asp Ser Val Gly
    610                 615                 620

Met Ala Arg Gly Tyr Trp Gly Gln Pro Ala Leu Thr Ala Glu Arg Phe
625                 630                 635                 640

Ile Ala Asn Pro Tyr Ala Ser Gln Pro Gly Ala Arg Leu Tyr Arg Thr
                645                 650                 655

Gly Asp Met Val Arg Val Leu Ala Asp Gly Ser Leu Glu Tyr Leu Gly
            660                 665                 670

Arg Arg Asp Tyr Glu Ile Lys Val Arg Gly His Arg Val Asp Val Arg
        675                 680                 685

Gln Val Glu Lys Val Ala Asn Ala His Pro Ala Ile Arg Gln Ala Val
    690                 695                 700

Val Ser Gly Trp Pro Leu Gly Ser Ser Asn Ala Gln Leu Val Ala Tyr
705                 710                 715                 720

Leu Val Pro Gln Ala Gly Ala Thr Val Gly Pro Arg Gln Val Arg Asp
                725                 730                 735

Tyr Leu Ala Glu Ser Leu Pro Ala Tyr Met Val Pro Thr Leu Tyr Thr
            740                 745                 750

Val Leu Glu Glu Leu Pro Arg Leu Pro Asn Gly Lys Leu Asp Arg Leu
        755                 760                 765

Ser Leu Pro Glu Pro Asp Leu Ser Ser Ser Arg Glu Glu Tyr Val Ala
    770                 775                 780

Pro His Gly Glu Val Glu Arg Lys Leu Ala Glu Ile Phe Gly Asn Leu
785                 790                 795                 800

Leu Gly Leu Glu His Val Gly Val His Asp Asn Phe Phe Ser Leu Gly
                805                 810                 815

Gly His Ser Leu Leu Ala Ala Gln Leu Ile Ser Arg Ile Arg Ala Thr
            820                 825                 830

Phe Arg Val Glu Val Ala Met Ala Thr Val Phe Glu Ser Pro Thr Val
        835                 840                 845

Glu Pro Leu Ala Arg His Ile Glu Glu Lys Leu Lys Asp Glu Ser Arg
    850                 855                 860

Val Gln Leu Ser Asn Val Val Pro Val Glu Arg Thr Gln Glu Ile Pro
865                 870                 875                 880

Leu Ser Tyr Leu Gln Glu Arg Leu Trp Phe Val His Glu His Met Lys
                885                 890                 895

Glu Gln Arg Thr Ser Tyr Asn Ile Thr Trp Thr Leu His Phe Ala Gly
            900                 905                 910

Lys Gly Phe Ser Val Glu Ala Leu Arg Thr Ala Phe Asp Glu Leu Val
        915                 920                 925

Ala Arg His Glu Thr Leu Arg Thr Trp Phe Gln Val Gly Glu Gly Thr
    930                 935                 940

Glu Gln Ala Val Gln Val Ile Gly Glu Pro Trp Ser Met Glu Leu Pro
945                 950                 955                 960
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Leu Arg Glu Val Ala Gly Thr Glu Val Thr Ala Ala Ile Asn Glu Met
               965                 970                 975

Ser Arg Gln Val Phe Asp Leu Arg Ala Gly Arg Leu Leu Thr Ala Ala
           980                 985                 990

Val Leu Arg Val Ala Glu Asp Glu  His Ile Leu Val Ser  Asn Ile His
        995                 1000                1005

His Ile  Ile Thr Asp Gly Trp  Ser Phe Gly Val Met  Leu Arg Glu
    1010                1015                1020

Leu Arg  Glu Leu Tyr Glu Ala  Ala Val Arg Gly Lys  Arg Ala Glu
    1025                1030                1035

Leu Pro  Pro Leu Thr Val Gln  Tyr Gly Asp Tyr Ala  Val Trp Gln
    1040                1045                1050

Arg Lys  Gln Asp Leu Ser Glu  His Leu Ala Tyr Trp  Lys Gly Lys
    1055                1060                1065

Val Glu  Glu Tyr Glu Asp Gly  Leu Glu Leu Pro Tyr  Asp Phe Pro
    1070                1075                1080

Arg Thr  Ser Asn Arg Ala Trp  Arg Ala Ala Thr Phe  Gln Tyr Ser
    1085                1090                1095

Tyr Pro  Pro Glu Leu Ala Arg  Lys Val Ala Glu Leu  Ser Arg Glu
    1100                1105                1110

Gln Gln  Ser Thr Leu Phe Met  Ser Leu Val Ala Ser  Leu Ala Val
    1115                1120                1125

Val Leu  Asn Arg Tyr Thr Gly  Arg Gln Asp Val Cys  Ile Gly Thr
    1130                1135                1140

Thr Val  Ala Gly Arg Ala Gln  Val Glu Leu Glu Ser  Leu Ile Gly
    1145                1150                1155

Phe Phe  Ile Asn Ile Leu Pro  Leu Arg Leu Asp Leu  Ser Gly Ala
    1160                1165                1170

Pro Ser  Leu His Glu Val Leu  Arg Arg Thr Lys Ala  Val Val Leu
    1175                1180                1185

Glu Gly  Phe Glu His Gln Glu  Leu Pro Phe Glu His  Leu Leu Lys
    1190                1195                1200

Ala Leu  Arg Arg Gln Arg Asp  Ser Ser Gln Ile Pro  Leu Val Pro
    1205                1210                1215

Val Val  Val Arg His Gln Asn  Phe Pro Met Ala Arg  Leu Glu Gly
    1220                1225                1230

Trp Ser  Glu Gly Val Glu Leu  Lys Lys Phe Glu Leu  Ala Gly Glu
    1235                1240                1245

Arg Thr  Thr Ala Ser Glu Gln  Asp Trp Gln Phe Phe  Gly Asp Gly
    1250                1255                1260

Ser Ser  Leu Glu Leu Ser Leu  Glu Tyr Ala Ala Glu  Leu Phe Ser
    1265                1270                1275

Glu Lys  Thr Val Arg Arg Met  Val Glu His His Gln  Arg Val Leu
    1280                1285                1290

Glu Ala  Leu Val Glu Gly Leu  Glu Glu Gly Leu His  Glu Val Arg
    1295                1300                1305

Leu Leu  Thr Glu Glu Glu Glu  Gly Leu His Gly Arg  Leu Asn Asp
    1310                1315                1320

Thr Ala  Arg Glu Leu Glu Glu  Arg Trp Ser Leu Ala  Glu Thr Phe
    1325                1330                1335
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Glu Arg  Gln Val Arg Glu Thr  Pro Glu Ala Val Ala  Cys Val Gly
    1340                1345                1350

Val Glu  Val Ala Thr Gly Gly  His Ser Arg Pro Thr  Tyr Arg Gln
    1355                1360                1365

Leu Thr  Tyr Arg Gln Leu Asn  Ala Arg Ala Asn Gln  Val Ala Arg
    1370                1375                1380

Arg Leu  Arg Ala Leu Gly Val  Gly Ala Glu Thr Arg  Val Ala Val
    1385                1390                1395

Leu Ser  Asp Arg Ser Pro Glu  Leu Leu Val Ala Met  Leu Ala Ile
    1400                1405                1410

Phe Lys  Ala Gly Gly Cys Tyr  Val Pro Val Asp Pro  Gln Tyr Pro
    1415                1420                1425

Gly His  Tyr Ile Glu Gln Ile  Leu Glu Asp Ala Ala  Pro Gln Val
    1430                1435                1440

Val Leu  Gly Lys Arg Gly Arg  Ala Asp Gly Val Arg  Val Asp Val
    1445                1450                1455

Trp Leu  Glu Leu Asp Gly Ala  Gln Arg Leu Thr Asp  Glu Ala Leu
    1460                1465                1470

Ala Ala  Gln Glu Glu Gly Glu  Leu Glu Gly Ala Glu  Arg Pro Glu
    1475                1480                1485

Ser Gln  Gln Leu Ala Cys Leu  Met Tyr Thr Ser Gly  Ser Thr Gly
    1490                1495                1500

Arg Pro  Lys Gly Val Met Val  Pro Tyr Ser Gln Leu  His Asn Trp
    1505                1510                1515

Leu Glu  Ala Gly Lys Glu Arg  Ser Pro Leu Glu Arg  Gly Glu Val
    1520                1525                1530

Met Leu  Gln Lys Thr Ala Ile  Ala Phe Ala Val Ser  Val Lys Glu
    1535                1540                1545

Leu Leu  Ser Gly Leu Leu Ala  Gly Val Ala Gln Val  Met Val Pro
    1550                1555                1560

Glu Thr  Leu Val Lys Asp Ser  Val Ala Leu Ala Gln  Glu Ile Glu
    1565                1570                1575

Arg Trp  Arg Val Thr Arg Ile  His Leu Val Pro Ser  His Leu Gly
    1580                1585                1590

Ala Leu  Leu Glu Gly Ala Gly  Glu Glu Ala Lys Gly  Leu Arg Ser
    1595                1600                1605

Leu Lys  Tyr Val Ile Thr Ala  Gly Glu Ala Leu Ala  Gln Gly Val
    1610                1615                1620

Arg Glu  Glu Ala Arg Arg Lys  Leu Pro Gly Ala Gln  Leu Trp Asn
    1625                1630                1635

Asn Tyr  Gly Cys Thr Glu Leu  Asn Asp Val Thr Tyr  His Pro Ala
    1640                1645                1650

Ser Glu  Gly Gly Gly Asp Thr  Val Phe Val Pro Ile  Gly Arg Pro
    1655                1660                1665

Ile Ala  Asn Thr Arg Val Tyr  Val Leu Asp Glu Gln  Leu Arg Arg
    1670                1675                1680

Val Pro  Val Gly Val Met Gly  Glu Leu Tyr Val Asp  Ser Val Gly
    1685                1690                1695

Met Ala  Arg Gly Tyr Trp Gly  Gln Pro Ala Leu Thr  Ala Glu Arg
    1700                1705                1710

Phe Ile  Ala Asn Pro Tyr Ala  Ser Gln Pro Gly Ala  Arg Leu Tyr
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    1715                1720                1725

Arg Thr  Gly Asp Met Val Arg  Val Leu Ala Asp Gly  Ser Leu Glu
    1730                1735                1740

Tyr Leu  Gly Arg Arg Asp Tyr  Glu Ile Lys Val Arg  Gly His Arg
    1745                1750                1755

Val Asp  Val Arg Gln Val Glu  Lys Val Ala Asn Ala  His Pro Ala
    1760                1765                1770

Ile Arg  Gln Ala Val Val Ser  Gly Trp Pro Leu Gly  Ser Ser Asn
    1775                1780                1785

Ala Gln  Leu Val Ala Tyr Leu  Val Pro Gln Ala Gly  Ala Thr Val
    1790                1795                1800

Gly Pro  Arg Gln Val Arg Asp  Tyr Leu Ala Glu Ser  Leu Pro Ala
    1805                1810                1815

Tyr Met  Val Pro Thr Leu Tyr  Thr Val Leu Glu Glu  Leu Pro Arg
    1820                1825                1830

Leu Pro  Asn Gly Lys Leu Asp  Arg Leu Ser Leu Pro  Glu Pro Asp
    1835                1840                1845

Leu Ser  Ser Ser Arg Glu Glu  Tyr Val Ala Pro His  Gly Glu Val
    1850                1855                1860

Glu Arg  Lys Leu Ala Glu Ile  Phe Gly Asn Leu Leu  Gly Leu Glu
    1865                1870                1875

His Val  Gly Val His Asp Asn  Phe Phe Ser Leu Gly  Gly His Ser
    1880                1885                1890

Leu Leu  Ala Ala Gln Val Val  Ser Arg Ile Gly Lys  Glu Leu Gly
    1895                1900                1905

Thr Gln  Ile Ser Ile Ala Asp  Leu Phe Gln Arg Pro  Thr Ile Glu
    1910                1915                1920

Gln Leu  Cys Glu Leu Ile Gly  Gly Leu Asp Asp Gln  Thr Gln Arg
    1925                1930                1935

Glu Leu  Ala Leu Ala Pro Ser  Gly Asn Thr Glu Ala  Val Leu Ser
    1940                1945                1950

Phe Ala  Gln Glu Arg Met Trp  Phe Leu His Asn Phe  Val Lys Gly
    1955                1960                1965

Met Pro  Tyr Asn Thr Pro Gly  Leu Asp His Leu Thr  Gly Glu Leu
    1970                1975                1980

Asp Val  Ala Ala Leu Glu Lys  Ala Ile Arg Ala Val  Ile Arg Arg
    1985                1990                1995

His Glu  Pro Leu Arg Thr Asn  Phe Val Glu Lys Asp  Gly Val Leu
    2000                2005                2010

Ser Gln  Leu Val Gly Thr Glu  Glu Arg Phe Arg Leu  Thr Val Thr
    2015                2020                2025

Pro Ile  Arg Asp Glu Ser Glu  Val Ala Arg Leu Met  Glu Ala Val
    2030                2035                2040

Ile Gln  Thr Pro Val Asp Leu  Glu Arg Glu Leu Met  Ile Arg Ala
    2045                2050                2055

Tyr Leu  Tyr Arg Val Asp Pro  Arg Asn His Tyr Leu  Phe Thr Thr
    2060                2065                2070

Ile His  His Ile Ala Phe Asp  Gly Trp Ser Thr Ser  Ile Phe Tyr
    2075                2080                2085

Arg Glu  Leu Ala Ala Tyr Tyr  Ala Ala Phe Leu Arg  Arg Glu Asp
    2090                2095                2100
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Ser Pro  Leu Pro Ala Leu Glu  Ile Ser Tyr Gln Asp  Tyr Ala Arg
    2105                2110                2115

Trp Glu  Arg Ala His Phe Gln  Asp Glu Val Leu Ala  Glu Lys Leu
    2120                2125                2130

Arg Tyr  Trp Arg Gln Arg Leu  Ser Gly Ala Arg Pro  Leu Val Leu
    2135                2140                2145

Pro Thr  Thr Tyr His Arg Pro  Pro Ile Gln Ser Phe  Ala Gly Ala
    2150                2155                2160

Val Val  Asn Phe Glu Ile Asp  Arg Ser Ile Thr Glu  Arg Leu Lys
    2165                2170                2175

Thr Leu  Phe Ala Glu Ser Gly  Thr Thr Met Tyr Met  Val Leu Leu
    2180                2185                2190

Gly Ala  Phe Ser Val Val Leu  Gln Arg Tyr Ser Gly  Gln Asp Asp
    2195                2200                2205

Ile Cys  Ile Gly Ser Pro Val  Ala Asn Arg Gly His  Ile Gln Thr
    2210                2215                2220

Glu Gly  Leu Ile Gly Leu Phe  Val Asn Thr Leu Val  Met Arg Val
    2225                2230                2235

Asp Ala  Ala Gly Asn Pro Arg  Phe Ile Asp Leu Leu  Ala Arg Ile
    2240                2245                2250

Gln Arg  Thr Ala Ile Asp Ala  Tyr Ala Asn Gln Glu  Val Pro Phe
    2255                2260                2265

Glu Lys  Ile Val Asp Asp Leu  Gln Val Ala Arg Asp  Thr Ala Arg
    2270                2275                2280

Ser Pro  Leu Val Gln Val Ile  Leu Asn Phe His Asn  Thr Pro Pro
    2285                2290                2295

Gln Ser  Glu Leu Glu Leu Gln  Gly Val Thr Leu Thr  Arg Met Pro
    2300                2305                2310

Val His  Asn Gly Thr Ala Lys  Phe Glu Leu Ser Ile  Asp Val Ala
    2315                2320                2325

Glu Thr  Ser Ala Gly Leu Thr  Gly Phe Val Glu Tyr  Ala Thr Asp
    2330                2335                2340

Leu Phe  Ser Glu Asn Phe Ile  Arg Arg Met Ile Gly  His Leu Glu
    2345                2350                2355

Val Val  Leu Asp Ala Val Gly  Arg Asp Pro Arg Ala  Pro Ile His
    2360                2365                2370

Glu Leu  Pro Leu Leu Thr Arg  Gln Asp Gln Leu Asp  Leu Leu Ser
    2375                2380                2385

Arg Ser  Gly His Thr Ala Pro  Ala Val Glu His Val  Glu Leu Ile
    2390                2395                2400

Pro His  Thr Phe Glu Arg Arg  Val Gln Glu Ser Pro  Gln Ala Ile
    2405                2410                2415

Ala Leu  Val Cys Gly Asp Glu  Arg Val Thr Tyr Ser  Ala Leu Asn
    2420                2425                2430

Arg Arg  Ala Ser Gln Ile Ala  Arg Arg Leu Arg Ala  Ala Gly Ile
    2435                2440                2445

Gly Pro  Asp Thr Leu Val Gly  Leu Cys Ala Gly Arg  Ser Ile Glu
    2450                2455                2460

Leu Val  Cys Gly Val Leu Gly  Ile Leu Lys Ala Gly  Gly Ala Tyr
    2465                2470                2475
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Val Pro  Ile Asp Pro Thr Ser  Ser Pro Glu Val Ile  Tyr Asp Val
    2480                 2485                 2490

Leu Tyr  Glu Ser Lys Val Arg  His Leu Leu Thr Glu  Ser Arg Leu
    2495                 2500                 2505

Val Gly  Gly Leu Pro Val Asp  Asp Gln Glu Ile Leu  Leu Leu Asp
    2510                 2515                 2520

Thr Pro  Ala Asp Gly Glu Gly  Asp Lys Ala Val Ala  Asp Arg Glu
    2525                 2530                 2535

Glu Pro  Pro Asp Leu Gly Glu  Val Ser Leu Thr Pro  Glu Cys Leu
    2540                 2545                 2550

Ala Tyr  Val Asn Phe Thr Ser  Asp Ser Gly Gly Ala  Pro Arg Gly
    2555                 2560                 2565

Ile Ala  Val Arg His Gly Ala  Leu Ala Arg Arg Met  Ala Ala Gly
    2570                 2575                 2580

His Ala  Gln Tyr Leu Ala Asn  Ser Ala Val Arg Phe  Leu Leu Lys
    2585                 2590                 2595

Ala Pro  Leu Thr Phe Asp Leu  Ala Val Ala Glu Leu  Phe Gln Trp
    2600                 2605                 2610

Ile Val  Ser Gly Gly Ser Leu  Ser Ile Leu Asp Pro  Asn Ala Asp
    2615                 2620                 2625

Arg Asp  Ala Ser Ala Phe Leu  Ala Gln Val Arg Arg  Asp Ser Ile
    2630                 2635                 2640

Gly Val  Leu Tyr Cys Val Pro  Ser Glu Leu Ser Thr  Leu Val Ser
    2645                 2650                 2655

His Leu  Glu Arg Glu Arg Glu  Arg Val His Glu Leu  Asn Thr Leu
    2660                 2665                 2670

Arg Phe  Ile Phe Cys Gly Gly  Asp Thr Leu Ala Val  Thr Val Val
    2675                 2680                 2685

Glu Arg  Leu Gly Val Leu Val  Arg Ala Gly Gln Leu  Pro Leu Arg
    2690                 2695                 2700

Leu Val  Asn Val Tyr Gly Thr  Lys Glu Thr Gly Ile  Gly Ala Gly
    2705                 2710                 2715

Cys Phe  Glu Cys Ala Leu Asp  Ala Asn Asp Pro Ser  Ala Glu Leu
    2720                 2725                 2730

Pro Pro  Gly Arg Leu Ser His  Glu Arg Met Pro Ile  Gly Gly Pro
    2735                 2740                 2745

Ala Gln  Asn Leu Trp Phe Tyr  Val Val Gln Pro Asn  Gly Gly Leu
    2750                 2755                 2760

Ala Pro  Leu Gly Ile Pro Gly  Glu Leu Tyr Val Gly  Gly Ala Gln
    2765                 2770                 2775

Leu Ala  Asp Ala Arg Phe Gly  Asp Glu Pro Thr Ala  Thr His Pro
    2780                 2785                 2790

Gly Phe  Val Pro Asn Pro Phe  Arg Ser Gly Ala Glu  Lys Asp Trp
    2795                 2800                 2805

Leu Tyr  Lys Thr Gly Asp Leu  Val Arg Trp Leu Pro  Gln Gly Pro
    2810                 2815                 2820

Leu Glu  Leu Val Ser Ala Ala  Arg Glu Arg Asp Gly  Gly Gly Asp
    2825                 2830                 2835

His Arg  Leu Asp Arg Gly Phe  Ile Glu Ala Arg Met  Arg Arg Val
    2840                 2845                 2850

Ala Ile  Val Arg Asp Ala Val  Val Ala Tyr Val Pro  Asp Arg Gln
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    2855                2860                2865

Asp Arg  Ala Arg Leu Val Ala  Tyr Val Val Leu Lys  Glu Ser Pro
    2870                2875                2880

Ala Ala  Asp Val Glu Pro Arg  Glu Gly Arg Glu Thr  Leu Lys Ala
    2885                2890                2895

Arg Ile  Ser Ala Glu Leu Gly  Ser Thr Leu Pro Glu  Tyr Met Leu
    2900                2905                2910

Pro Ala  Ala Tyr Val Phe Met  Asp Ser Leu Pro Leu  Thr Ala Tyr
    2915                2920                2925

Gly Arg  Ile Asp Arg Lys Ala  Leu Pro Glu Pro Glu  Asp Asp Arg
    2930                2935                2940

His Gly  Gly Ser Ala Ile Ala  Tyr Val Ala Pro Arg  Gly Pro Thr
    2945                2950                2955

Glu Lys  Ala Leu Ala His Ile  Trp Gln Gln Val Leu  Lys Arg Pro
    2960                2965                2970

Gln Val  Gly Leu Arg Asp Asn  Phe Phe Glu Leu Gly  Gly His Ser
    2975                2980                2985

Val Ala  Ala Ile Gln Leu Val  Ser Val Ser Arg Lys  His Leu Glu
    2990                2995                3000

Val Glu  Val Pro Leu Ser Leu  Ile Phe Glu Ser Pro  Val Leu Glu
    3005                3010                3015

Ala Met  Ala Arg Gly Ile Glu  Ala Leu Gln Gln Gln  Gly Arg Ser
    3020                3025                3030

Gly Ala  Val Ser Ser Ile His  Arg Val Glu Arg Thr  Gly Pro Leu
    3035                3040                3045

Pro Leu  Ala Tyr Val Gln Glu  Arg Leu Trp Phe Val  His Glu His
    3050                3055                3060

Met Lys  Glu Gln Arg Thr Ser  Tyr Asn Ile Thr Trp  Thr Leu His
    3065                3070                3075

Phe Ala  Gly Lys Gly Phe Ser  Val Glu Ala Leu Arg  Thr Ala Phe
    3080                3085                3090

Asp Glu  Leu Val Ala Arg His  Glu Thr Leu Arg Thr  Trp Phe Gln
    3095                3100                3105

Val Gly  Glu Gly Thr Glu Gln  Ala Val Gln Val Ile  Gly Glu Pro
    3110                3115                3120

Trp Ser  Met Glu Leu Pro Leu  Arg Glu Val Ala Gly  Thr Glu Val
    3125                3130                3135

Thr Ala  Ala Ile Asn Glu Met  Ser Arg Gln Val Phe  Asp Leu Arg
    3140                3145                3150

Ala Gly  Arg Leu Leu Thr Ala  Ala Val Leu Arg Val  Ala Glu Asp
    3155                3160                3165

Glu His  Ile Leu Val Ser Asn  Ile His His Ile Ile  Thr Asp Gly
    3170                3175                3180

Trp Ser  Phe Gly Val Met Leu  Arg Glu Leu Arg Glu  Leu Tyr Glu
    3185                3190                3195

Ala Ala  Val Arg Gly Glu Arg  Ala Glu Leu Pro Pro  Leu Thr Val
    3200                3205                3210

Gln Tyr  Gly Asp Tyr Ala Val  Trp Gln Arg Lys Gln  Asp Leu Ser
    3215                3220                3225

Glu His  Leu Ala Tyr Trp Lys  Gly Lys Val Glu Gly  Asp Glu Asp
    3230                3235                3240
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Gly Leu  Glu Leu Pro Tyr Asp  Phe Pro Arg Thr Ser  Asn Arg Ala
    3245                3250                3255

Trp Arg  Ala Ala Thr Phe Gln  Tyr Ser Tyr His Pro  Glu Leu Ala
    3260                3265                3270

Arg Lys  Val Ala Glu Leu Ser  Arg Glu Gln Gln Ser  Thr Leu Phe
    3275                3280                3285

Met Ser  Leu Val Ala Ser Leu  Ala Val Val Leu Asn  Arg Tyr Thr
    3290                3295                3300

Gly Arg  Glu Asp Leu Cys Ile  Gly Thr Thr Val Ala  Gly Arg Ala
    3305                3310                3315

Gln Val  Glu Leu Glu Ser Leu  Ile Gly Phe Phe Ile  Asn Ile Leu
    3320                3325                3330

Pro Leu  Arg Leu Asp Leu Ser  Gly Ala Pro Ser Leu  His Glu Val
    3335                3340                3345

Leu Arg  Arg Thr Lys Val Val  Val Leu Glu Gly Phe  Glu His Gln
    3350                3355                3360

Glu Leu  Pro Phe Glu His Leu  Leu Lys Ala Leu Arg  Arg Gln Arg
    3365                3370                3375

Asp Ser  Ser Gln Ile Pro Leu  Val Pro Val Val Val  Arg His Gln
    3380                3385                3390

Asn Phe  Pro Met Ala Arg Leu  Glu Gly Trp Ser Glu  Gly Val Glu
    3395                3400                3405

Leu Lys  Lys Phe Glu Leu Ala  Gly Glu Arg Thr Thr  Ala Ser Glu
    3410                3415                3420

Gln Asp  Trp Gln Phe Phe Gly  Asp Gly Ser Ser Leu  Glu Leu Ser
    3425                3430                3435

Leu Glu  Tyr Ala Ala Glu Leu  Phe Ser Glu Lys Thr  Val Arg Arg
    3440                3445                3450

Met Val  Glu His His Gln Arg  Val Leu Glu Ala Leu  Val Glu Gly
    3455                3460                3465

Leu Glu  Glu Gly Leu His Glu  Val Arg Leu Leu Thr  Glu Glu Glu
    3470                3475                3480

Glu Gly  Leu His Gly Arg Leu  Asn Asp Thr Ala Arg  Glu Leu Glu
    3485                3490                3495

Glu Arg  Trp Ser Leu Ala Glu  Thr Phe Glu Arg Gln  Val Arg Glu
    3500                3505                3510

Thr Pro  Glu Ala Val Ala Cys  Val Gly Val Glu Val  Ala Thr Gly
    3515                3520                3525

Gly His  Ser Arg Pro Thr Tyr  Arg Gln Leu Thr Tyr  Arg Gln Leu
    3530                3535                3540

Asn Ala  Arg Ala Asn Gln Val  Ala Arg Arg Leu Arg  Ala Leu Gly
    3545                3550                3555

Val Gly  Ala Glu Thr Arg Val  Ala Val Leu Ser Asp  Arg Ser Pro
    3560                3565                3570

Glu Leu  Leu Val Ala Met Leu  Ala Ile Phe Lys Ala  Gly Gly Cys
    3575                3580                3585

Tyr Val  Pro Val Asp Pro Gln  Tyr Pro Gly Ser Tyr  Ile Glu Gln
    3590                3595                3600

Ile Leu  Glu Asp Ala Ala Pro  Gln Val Val Leu Gly  Lys Arg Gly
    3605                3610                3615
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Arg Ala  Asp Gly Val Arg Val  Asp Val Trp Leu Glu  Leu Asp Gly
    3620                3625                3630

Ala Gln  Arg Leu Thr Asp Glu  Ala Leu Ala Ala Gln  Glu Glu Gly
    3635                3640                3645

Glu Leu  Glu Gly Ala Glu Arg  Pro Glu Ser Gln Gln  Leu Ala Cys
    3650                3655                3660

Leu Met  Tyr Thr Ser Gly Ser  Thr Gly Arg Pro Lys  Gly Val Met
    3665                3670                3675

Val Pro  Tyr Ser Gln Leu His  Asn Trp Leu Glu Ala  Gly Lys Glu
    3680                3685                3690

Arg Ser  Pro Leu Glu Arg Gly  Glu Val Met Leu Gln  Lys Thr Ala
    3695                3700                3705

Ile Ala  Phe Ala Val Ser Val  Lys Glu Leu Leu Ser  Gly Leu Leu
    3710                3715                3720

Ala Gly  Val Ala Gln Val Met  Val Pro Glu Thr Leu  Val Lys Asp
    3725                3730                3735

Ser Val  Ala Leu Ala Gln Glu  Ile Glu Arg Trp Arg  Val Thr Arg
    3740                3745                3750

Ile His  Leu Val Pro Ser His  Leu Gly Ala Leu Leu  Glu Gly Ala
    3755                3760                3765

Gly Glu  Glu Ala Lys Gly Leu  Arg Ser Leu Lys Tyr  Val Ile Thr
    3770                3775                3780

Ala Gly  Glu Ala Leu Ala Gln  Gly Val Arg Glu Glu  Ala Arg Arg
    3785                3790                3795

Lys Leu  Pro Gly Ala Gln Leu  Trp Asn Asn Tyr Gly  Cys Thr Glu
    3800                3805                3810

Leu Asn  Asp Val Thr Tyr His  Pro Ala Ser Glu Gly  Gly Gly Asp
    3815                3820                3825

Thr Val  Phe Val Pro Ile Gly  Arg Pro Ile Ala Asn  Thr Arg Val
    3830                3835                3840

Tyr Val  Leu Asp Glu Gln Leu  Arg Arg Val Pro Val  Gly Val Met
    3845                3850                3855

Gly Glu  Leu Tyr Val Asp Ser  Val Gly Met Ala Arg  Gly Tyr Trp
    3860                3865                3870

Gly Gln  Pro Ala Leu Thr Ala  Glu Arg Phe Ile Ala  Asn Pro Tyr
    3875                3880                3885

Ala Ser  Gln Pro Gly Ala Arg  Leu Tyr Arg Thr Gly  Asp Met Val
    3890                3895                3900

Arg Val  Leu Ala Asp Gly Ser  Leu Glu Tyr Leu Gly  Arg Arg Asp
    3905                3910                3915

Tyr Glu  Ile Lys Val Arg Gly  His Arg Val Asp Val  Arg Gln Val
    3920                3925                3930

Glu Lys  Val Ala Asn Ala His  Pro Ala Ile Arg Gln  Ala Val Val
    3935                3940                3945

Ser Gly  Trp Pro Leu Gly Ser  Ser Asn Ala Gln Leu  Val Ala Tyr
    3950                3955                3960

Leu Val  Pro Gln Ala Gly Ala  Thr Val Gly Pro Arg  Gln Val Arg
    3965                3970                3975

Asp Tyr  Leu Ala Glu Ser Leu  Pro Ala Tyr Met Val  Pro Thr Leu
    3980                3985                3990

Tyr Thr  Val Leu Glu Glu Leu  Pro Arg Leu Pro Asn  Gly Lys Leu
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    3995                4000                4005

Asp Arg  Leu Ser Leu Pro Glu  Pro Asp Leu Ser Ser  Ser Arg Glu
    4010                4015                4020

Glu Tyr  Val Ala Pro His Gly  Glu Val Glu Arg Lys  Leu Ala Glu
    4025                4030                4035

Ile Phe  Gly Asn Leu Leu Gly  Leu Glu His Val Gly  Val His Asp
    4040                4045                4050

Asn Phe  Phe Asn Leu Gly Gly  His Ser Leu Leu Ala  Ser Gln Leu
    4055                4060                4065

Ile Ser  Arg Ile Arg Ala Thr  Phe Arg Val Glu Val  Ala Met Ala
    4070                4075                4080

Thr Val  Phe Glu Ser Pro Thr  Val Glu Pro Leu Ala  Arg His Ile
    4085                4090                4095

Glu Glu  Lys Leu Lys Asp Glu  Ser Arg Val Gln Leu  Ser Asn Val
    4100                4105                4110

Val Pro  Val Glu Arg Thr Gln  Glu Leu Pro Leu Ser  Tyr Leu Gln
    4115                4120                4125

Glu Arg  Leu Trp Phe Val His  Glu His Met Lys Glu  Gln Arg Thr
    4130                4135                4140

Ser Tyr  Asn Gly Thr Ile Gly  Leu Arg Leu Arg Gly  Pro Leu Ser
    4145                4150                4155

Ile Pro  Ala Leu Arg Ala Thr  Phe His Asp Leu Val  Ala Arg His
    4160                4165                4170

Glu Ser  Leu Arg Thr Val Phe  Arg Val Pro Glu Gly  Arg Thr Thr
    4175                4180                4185

Pro Val  Gln Val Ile Leu Asp  Ser Met Asp Leu Asp  Ile Pro Val
    4190                4195                4200

Arg Asp  Ala Thr Glu Ala Asp  Ile Ile Pro Gly Met  Asp Glu Leu
    4205                4210                4215

Ala Gly  His Ile Tyr Asp Met  Glu Lys Gly Pro Leu  Phe Met Val
    4220                4225                4230

Arg Leu  Leu Arg Leu Ala Glu  Asp Ser His Val Leu  Leu Met Gly
    4235                4240                4245

Met His  His Ile Val Tyr Asp  Ala Trp Ser Gln Phe  Asn Val Met
    4250                4255                4260

Ser Arg  Asp Ile Asn Leu Leu  Tyr Ser Ala His Val  Thr Gly Ile
    4265                4270                4275

Glu Ala  Arg Leu Pro Ala Leu  Pro Ile Gln Tyr Ala  Asp Phe Ser
    4280                4285                4290

Val Trp  Gln Arg Gln Gln Asp  Phe Arg His His Leu  Asp Tyr Trp
    4295                4300                4305

Lys Ser  Thr Leu Gly Asp Tyr  Arg Asp Asp Leu Glu  Leu Pro Tyr
    4310                4315                4320

Asp Tyr  Pro Arg Pro Pro Ser  Arg Thr Trp His Ala  Thr Arg Phe
    4325                4330                4335

Thr Phe  Arg Tyr Pro Asp Ala  Leu Ala Arg Ala Phe  Ala Arg Phe
    4340                4345                4350

Asn Gln  Ser His Gln Ser Thr  Leu Phe Met Gly Leu  Leu Thr Ser
    4355                4360                4365

Phe Ala  Ile Val Leu Arg His  Tyr Thr Gly Arg Asn  Asp Ile Cys
    4370                4375                4380
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Ile Gly  Thr Thr Thr Ala Gly  Arg Ala Gln Leu Glu  Leu Glu Asn
    4385                4390                4395

Leu Val  Gly Phe Phe Ile Asn  Ile Leu Pro Leu Arg  Ile Asn Leu
    4400                4405                4410

Ala Gly  Asp Pro Asp Ile Ser  Glu Leu Met Asn Arg  Ala Lys Lys
    4415                4420                4425

Ser Val  Leu Gly Ala Phe Glu  His Gln Ala Leu Pro  Phe Glu Arg
    4430                4435                4440

Leu Leu  Ser Ala Leu Asn Lys  Gln Arg Asp Ser Ser  His Ile Pro
    4445                4450                4455

Leu Val  Pro Val Met Leu Arg  His Gln Asn Phe Pro  Thr Ala Met
    4460                4465                4470

Thr Gly  Lys Trp Ala Asp Gly  Val Asp Met Glu Val  Ile Glu Arg
    4475                4480                4485

Asp Glu  Arg Thr Thr Pro Asn  Glu Leu Asp Leu Gln  Phe Phe Gly
    4490                4495                4500

Asp Asp  Thr Tyr Leu His Ala  Val Val Glu Phe Pro  Ala Gln Leu
    4505                4510                4515

Phe Ser  Glu Val Thr Val Arg  Arg Leu Met Gln Arg  His Gln Lys
    4520                4525                4530

Val Ile  Glu Phe Met Cys Ala  Thr Leu Gly Ala Arg
    4535                4540                4545


<210> SEQ ID NO 51
<211> LENGTH: 1023
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1023)
<223> OTHER INFORMATION: CysL

<400> SEQUENCE: 51

Val Asn Val Leu Ala Arg His Ser Thr Gly Ser His Asp Glu Pro Val
1               5                  10                  15

Ala Gly Asp Val Glu Leu Arg Val Gly Gly Pro Gly Val Pro Asp Ala
            20                  25                  30

His Ser Ser Glu Ser Val Glu Val Leu Ala Arg Trp Leu Arg Thr Ala
        35                  40                  45

Glu Glu Lys Tyr Pro Gly Val Met Gly Pro Ile Arg Gln Glu Gly Pro
    50                  55                  60

Trp Phe Ala Ile Pro Leu Thr Cys Pro Arg Gly Ala Arg Ser Ala Arg
65                  70                  75                  80

Phe Gly Leu Trp Leu Gly Glu Leu Asp Arg Gln Gly Gln Leu Leu His
                85                  90                  95

Met Val Ala Ser Tyr Leu Ala Ala Val His His Val Leu Val Ser Val
            100                 105                 110

Arg Glu Pro Ser Ala Asn Val Leu Glu Val Leu Val Ser Asp Ser Thr
        115                 120                 125

Thr Pro Ser Gly Leu Asn Arg Phe Leu Asn Gly Leu Asp Ser Val Leu
    130                 135                 140

Glu Ile Leu Ala His Gly Arg Ser Asp Leu Leu Leu Gln His Leu Thr
145                 150                 155                 160
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Gly Arg Leu Pro Pro Asp Glu Met Pro Phe Val Glu Asp Arg Glu Glu
                165                 170                 175

Arg Glu Glu His Pro Ala Thr Asp Val Glu Ala Asp Ala Val Val Ser
            180                 185                 190

Val Leu Phe Gln Pro Val Asp Phe Pro Ser Leu Ala Arg Leu Asp Ala
        195                 200                 205

Ser Leu Leu Ala Tyr Asp Asp Glu Asp Ala Gly Ala Val Gly Arg Val
    210                 215                 220

Leu Gly Glu Leu Leu Gln Pro Phe Leu Leu Asp Ser Ala Arg Met Thr
225                 230                 235                 240

Val Gly Arg Lys Ala Val Arg Val Asp His Ile Cys Leu Pro Gly Leu
                245                 250                 255

Leu Arg Ala Asp Ser Arg Ala Ala Glu Glu Ser Val Leu Ala Pro Ala
            260                 265                 270

Leu Arg Leu Ala Thr Lys Pro Gly Arg His Phe Val Ala Leu Cys Arg
        275                 280                 285

Asn Thr Ala Leu Arg Leu Gly Asp Arg Leu Pro His Leu Leu Ala Gln
    290                 295                 300

Gly Pro Leu Cys Asp Gly Ala Ser Thr Ala Leu Leu Leu Leu Gln Arg
305                 310                 315                 320

Val Leu Asp Thr Leu Ile Gly Ser Gly Gly Leu Lys Asp His Arg Leu
                325                 330                 335

Thr Leu Glu Leu Val Gly Ala Asp Pro Arg Thr Glu Ala Ala Phe Arg
            340                 345                 350

Ala Arg Thr Pro Trp Leu Val Ala Glu Arg Ala Ala Ser Ala Ala Ser
        355                 360                 365

Thr Asp Ala Pro Arg Val Asp Val Val Val Leu Phe Pro Ala Ala Arg
    370                 375                 380

Pro Ser Ala Leu Glu Leu Arg Pro Asp Ser Val Val Ile Asp Leu Phe
385                 390                 395                 400

Gly Thr Trp Ser Leu Arg Pro Arg Pro Glu Val Leu Ala Lys Asn Ile
                405                 410                 415

Val Tyr Val Arg Gly Ala Ser Val Arg Leu Ala Gly Glu Ala Val Val
            420                 425                 430

Ser Thr Pro Ser Phe Ala Pro Asp Arg Val Glu Pro Ala Leu Leu Glu
        435                 440                 445

Ala Leu Leu Arg Glu Leu Asp Ala Glu Ala Ser Ser Asp Gly Leu Ala
    450                 455                 460

His Glu His Arg Leu Glu Ile Gly Gly Ile Arg Gly Phe Trp Gly Glu
465                 470                 475                 480

Ile Arg Arg Ala Glu Trp Asp Ala Phe His Ser Arg Arg Arg Gly Glu
                485                 490                 495

Leu Ala Arg Phe Gln Val Ser Gly Gln Val Thr Ala Ala Asn Pro Gly
            500                 505                 510

Leu Ala Ser Leu Pro Asp Gly Ala Thr Asn Ile Cys Glu Tyr Ile Phe
        515                 520                 525

Arg Glu Ala His Leu Arg Ser Gly Ser Cys Leu Val Asp Pro Gln Ser
    530                 535                 540

Gly Gln Ser Ala Thr Tyr Ala Glu Leu Arg Arg Leu Ala Ala Ala Tyr
545                 550                 555                 560

Ala Arg Arg Phe Arg Ala Leu Gly Leu Arg Gln Gly Asp Val Val Ala
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               565                 570                 575

Leu Ala Ala Pro Asp Gly Ile Ser Ser Val Ala Val Met Leu Gly Cys
            580                 585                 590

Phe Leu Gly Gly Trp Val Phe Ala Pro Leu Asn His Thr Ala Ser Ala
        595                 600                 605

Val Asn Phe Glu Ala Met Leu Ser Ser Ala Ser Pro Arg Leu Val Leu
    610                 615                 620

His Ala Ala Ser Thr Val Ala Arg His Leu Pro Val Leu Ser Thr Arg
625                 630                 635                 640

Arg Cys Ala Glu Leu Ala Ser Phe Leu Pro Pro Asp Ala Leu Asp Gly
                645                 650                 655

Val Glu Gly Asp Val Thr Pro Leu Pro Val Ser Pro Glu Ala Pro Ala
            660                 665                 670

Val Met Leu Phe Thr Ser Gly Ser Thr Gly Gly Pro Lys Ala Val Thr
        675                 680                 685

His Thr His Ala Asp Phe Ile Thr Cys Ser Arg Asn Tyr Ala Pro Tyr
    690                 695                 700

Val Val Glu Leu Arg Pro Asp Asp Arg Val Tyr Thr Pro Ser Pro Thr
705                 710                 715                 720

Phe Phe Ala Tyr Gly Leu Asn Asn Leu Leu Leu Ser Leu Ser Ala Gly
                725                 730                 735

Ala Thr His Val Ile Ser Val Pro Arg Asn Gly Gly Met Gly Val Ala
            740                 745                 750

Glu Ile Leu Ala Arg Asn Glu Val Thr Val Leu Phe Ala Val Pro Ala
        755                 760                 765

Val Tyr Lys Leu Ile Ile Ser Lys Asn Asp Arg Gly Leu Arg Leu Pro
    770                 775                 780

Lys Leu Arg Leu Cys Ile Ser Ala Gly Glu Lys Leu Pro Leu Lys Leu
785                 790                 795                 800

Tyr Arg Glu Ala Arg Ser Phe Phe Ser Val Asn Val Leu Asp Gly Ile
                805                 810                 815

Gly Cys Thr Glu Ala Ile Ser Thr Phe Ile Ser Asn Arg Glu Ser Tyr
            820                 825                 830

Val Ala Pro Gly Cys Thr Gly Val Val Val Pro Gly Phe Glu Val Lys
        835                 840                 845

Leu Val Asn Pro Arg Gly Glu Leu Cys Arg Val Gly Glu Val Gly Val
    850                 855                 860

Leu Trp Val Arg Gly Gly Ala Leu Thr Arg Gly Tyr Val Asn Ala Pro
865                 870                 875                 880

Asp Leu Thr Glu Lys His Phe Val Asp Gly Trp Phe Asn Thr Gln Asp
                885                 890                 895

Met Phe Phe Met Asp Ala Glu Tyr Arg Leu Tyr Asn Val Gly Arg Ala
            900                 905                 910

Gly Ser Val Ile Lys Ile Asn Ser Cys Trp Phe Ser Pro Glu Met Met
        915                 920                 925

Glu Ser Val Leu Gln Ser His Pro Ala Val Lys Glu Cys Ala Val Cys
    930                 935                 940

Val Val Ile Asp Asp Tyr Gly Leu Pro Arg Pro Lys Ala Phe Ile Val
945                 950                 955                 960

Thr Gly Glu His Glu Arg Ser Glu Pro Glu Leu Glu His Leu Trp Ala
                965                 970                 975
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Glu Leu Arg Val Leu Ser Lys Glu Lys Leu Gly Lys Asp His Tyr Pro
            980                 985                 990

His Leu Phe Ala Thr Ile Lys Thr  Leu Pro Arg Thr Ser  Ser Gly Lys
        995                 1000                1005

Leu Met  Arg Ser Glu Leu Ala  Lys Leu Leu Thr Ser  Gly Pro Pro
    1010                1015                1020


<210> SEQ ID NO 52
<211> LENGTH: 38
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(38)
<223> OTHER INFORMATION: CysM

<400> SEQUENCE: 52

Met Asn Pro Lys Phe Leu Gly Gly Leu Gly Ala Gly Val Cys Ile Ala
1               5                   10                  15

Ser Leu Phe Gln Thr Val Met Arg Thr Val Pro Leu Lys Asp Ala Gly
            20                  25                  30

Ser Gly Asp Arg Ala Cys
        35


<210> SEQ ID NO 53
<211> LENGTH: 357
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(357)
<223> OTHER INFORMATION: CysN

<400> SEQUENCE: 53

Met Ser Thr Arg Thr Lys Asn Phe Asn Val Met Gly Ile Asp Trp Met
1               5                   10                  15

Pro Ser Ser Ala Glu Phe Lys Arg Arg Val Pro Arg Thr Gln Arg Ala
            20                  25                  30

Ala Glu Ala Val Leu Ala Gly Arg Arg Cys Leu Met Asp Ile Leu Asp
        35                  40                  45

Arg Gly Asp Pro Arg Leu Phe Val Ile Val Gly Pro Cys Ser Ile His
    50                  55                  60

Asp Pro Val Ala Gly Leu Asp Tyr Ala Lys Arg Leu Arg Lys Leu Ala
65                  70                  75                  80

Asp Glu Val Arg Glu Thr Leu Phe Val Val Met Arg Val Tyr Phe Glu
                85                  90                  95

Lys Pro Arg Thr Thr Thr Gly Trp Lys Gly Phe Ile Asn Asp Pro Arg
            100                 105                 110

Met Asp Gly Ser Phe His Ile Glu Glu Gly Met Glu Arg Gly Arg Arg
        115                 120                 125

Phe Leu Leu Asp Val Ala Glu Glu Gly Leu Pro Ala Ala Thr Glu Ala
    130                 135                 140

Leu Asp Pro Ile Ala Ser Gln Tyr Tyr Gly Asp Leu Ile Ser Trp Thr
145                 150                 155                 160

Ala Ile Gly Ala Arg Thr Ala Glu Ser Gln Thr His Arg Glu Met Ala
                165                 170                 175
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Ser Gly Leu Ser Thr Pro Val Gly Phe Lys Asn Gly Thr Asp Gly Ser
            180                 185                 190

Leu Asp Ala Ala Val Asn Gly Ile Ile Ser Ala Ser His Pro His Ser
        195                 200                 205

Phe Leu Gly Val Ser Glu Asn Gly Ala Cys Ala Ile Ile Arg Thr Arg
    210                 215                 220

Gly Asn Thr Tyr Gly His Leu Val Leu Arg Gly Gly Gly Gly Arg Pro
225                 230                 235                 240

Asn Tyr Asp Ala Val Ser Val Ala Leu Ala Glu Lys Ala Leu Ala Lys
                245                 250                 255

Ala Arg Leu Pro Thr Asn Ile Val Val Asp Cys Ser His Ala Asn Ser
            260                 265                 270

Trp Lys Asn Pro Glu Leu Gln Pro Leu Val Met Arg Asp Val Val His
        275                 280                 285

Gln Ile Arg Glu Gly Asn Arg Ser Val Val Gly Leu Met Ile Glu Ser
    290                 295                 300

Phe Ile Glu Ala Gly Asn Gln Pro Ile Pro Ala Asp Leu Ser Gln Leu
305                 310                 315                 320

Arg Tyr Gly Cys Ser Val Thr Asp Ala Cys Val Asp Trp Lys Thr Thr
                325                 330                 335

Glu Lys Met Leu Tyr Ser Ala His Glu Glu Leu Leu His Ile Leu Pro
            340                 345                 350

Arg Ser Lys Val Ala
        355


<210> SEQ ID NO 54
<211> LENGTH: 203
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(203)
<223> OTHER INFORMATION: CysO

<400> SEQUENCE: 54

Met Pro Ala Arg Ser Thr Pro Ser Leu Glu Ser Gly Asp Phe Phe Ala
1               5                   10                  15

Asp Val Thr Phe Ser Asp Leu Ser Ile Glu Ser Ala Asp Leu Ser Gly
            20                  25                  30

Lys Glu Phe Glu Arg Cys Thr Phe Arg Arg Cys Lys Leu Pro Glu Ser
        35                  40                  45

Arg Trp Val Arg Ser Arg Leu Glu Asp Cys Val Phe Glu Gly Cys Asp
    50                  55                  60

Leu Leu Arg Met Val Pro Glu Lys Leu Ala Leu Arg Ser Val Thr Phe
65                  70                  75                  80

Lys Asp Thr Arg Leu Met Gly Val Asp Trp Ser Gly Leu Gly Thr Met
                85                  90                  95

Pro Asp Val Gln Phe Glu Gln Cys Asp Leu Arg Tyr Ser Ser Phe Leu
            100                 105                 110

Lys Leu Asn Leu Arg Lys Thr Arg Phe Val Gly Cys Ser Ala Arg Glu
        115                 120                 125

Ala Asn Phe Ile Asp Val Asp Leu Ala Glu Ser Asp Phe Thr Gly Thr
    130                 135                 140

Asp Met Pro Gly Cys Thr Met Gln Gly Cys Val Leu Thr Lys Thr Asn
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145                 150                 155                 160

Phe Ala Arg Ser Thr Asn Phe Ile Phe Asp Pro Lys Ala Asn Gln Val
                165                 170                 175

Lys Gly Thr Arg Val Gly Val Glu Thr Ala Val Ala Leu Ala Gln Ala
            180                 185                 190

Leu Gly Met Val Val Asp Gly Tyr Gln Thr Pro
        195                 200


<210> SEQ ID NO 55
<211> LENGTH: 233
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(233)
<223> OTHER INFORMATION: CysP

<400> SEQUENCE: 55

Met Lys Arg Phe Phe Lys Leu Gln Leu Arg Thr Thr Asn Val Pro Ala
1               5                   10                  15

Ala Arg Ala Phe Tyr Thr Ala Leu Phe Gly Glu Gly Ala Ala Asn Ala
            20                  25                  30

Asp Ile Val Pro Leu Pro Glu Gln Ala Ile Ala Arg Gly Ala Pro Ala
        35                  40                  45

His Trp Leu Gly Tyr Val Gly Val Glu Asp Val Asp Glu Ala Val Arg
    50                  55                  60

Ser Phe Val Gly Arg Gly Ala Thr Gln Leu Gly Pro Thr His Pro Thr
65                  70                  75                  80

Asn Asp Gly Gly Arg Val Ala Ile Leu Arg Asp Pro Gly Gly Ala Thr
                85                  90                  95

Phe Ala Val Ala Thr Ala Pro Ala Thr Thr Arg Ala Leu Gln Pro Glu
            100                 105                 110

Val Val Trp Gln Gln Leu Tyr Ala Ala Asn Val Gln Gln Thr Ala Ala
        115                 120                 125

Ser Tyr Cys Asp Leu Phe Gly Trp Arg Leu Ser Asp Arg Arg Asp Leu
    130                 135                 140

Gly Ala Leu Gly Val His Gln Glu Phe Thr Trp Arg Ser Asp Glu Pro
145                 150                 155                 160

Ser Ala Gly Ser Val Val Asp Val Ala Gly Leu Lys Gly Val His Ser
                165                 170                 175

His Trp Leu Phe His Phe Arg Val Ala Ala Leu Asp Pro Ala Met Glu
            180                 185                 190

Val Val Arg Lys Ala Gly Gly Val Val Ile Gly Pro Met Glu Leu Pro
        195                 200                 205

Asn Gly Asp Arg Ile Ala Val Cys Glu Asp Pro Gln Arg Ala Ala Phe
    210                 215                 220

Ala Leu Arg Glu Ser Ser His Gly Arg
225                 230


<210> SEQ ID NO 56
<211> LENGTH: 264
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(264)
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<223> OTHER INFORMATION: CysQ

<400> SEQUENCE: 56

Met Gln Glu Ile Gly Gln Thr Ala Leu Trp Val Ala Gly Met Arg Ala
1 5 10 15

Leu Glu Thr Glu Arg Ser Asn Pro Leu Phe Arg Asp Pro Phe Ala Arg
20 25 30

Arg Leu Ala Gly Asp Thr Leu Val Glu Glu Leu Arg Arg Arg Asn Ala
35 40 45

Gly Glu Gly Ala Met Pro Pro Ala Ile Glu Val Arg Thr Arg Trp Leu
50 55 60

Asp Asp Gln Ile Thr Leu Gly Leu Gly Arg Gly Ile Arg Gln Ile Val
65 70 75 80

Ile Leu Ala Ala Gly Met Asp Ala Arg Ala Tyr Arg Leu Ala Trp Pro
85 90 95

Gly Asp Thr Arg Leu Phe Glu Leu Asp His Asp Ala Val Leu Gln Asp
100 105 110

Lys Glu Ala Lys Leu Thr Gly Val Ala Pro Lys Cys Glu Arg His Ala
115 120 125

Val Ser Val Asp Leu Ala Asp Asp Trp Pro Ala Ala Leu Lys Lys Ser
130 135 140

Gly Phe Asp Pro Gly Val Pro Thr Leu Trp Leu Ile Glu Gly Leu Leu
145 150 155 160

Val Tyr Leu Thr Glu Ala Gln Val Thr Leu Leu Met Ala Arg Val Asn
165 170 175

Ala Leu Ser Val Pro Glu Ser Ile Val Leu Ile Asp Val Val Gly Arg
180 185 190

Ser Ile Leu Asp Ser Ser Arg Val Lys Leu Met His Asp Leu Ala Arg
195 200 205

Gln Phe Gly Thr Asp Glu Pro Glu Val Ile Leu Arg Pro Ile Gly Trp
210 215 220

Asp Pro His Val Tyr Thr Thr Ala Ala Ile Gly Lys Gln Leu Gly Arg
225 230 235 240

Trp Pro Phe Pro Val Ala Pro Arg Gly Thr Pro Gly Val Pro Gln Gly
245 250 255

Tyr Leu Val His Gly Val Lys Arg
260

<210> SEQ ID NO 57
<211> LENGTH: 333
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(333)
<223> OTHER INFORMATION: CysR

<400> SEQUENCE: 57

Val Asn Gly Thr Thr Gly Lys Thr Gly Leu Val Ala Glu Arg Ser Gly
1 5 10 15

Ala Ile Ser Pro Arg Asp Tyr Lys Ser Lys Glu Leu Val Trp Asp Ser
20 25 30

Leu Ala Ala Thr Arg Ser Lys Pro Arg Arg Val Leu Pro Glu Gly Asp
35 40 45

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Val Val Gly His Leu Tyr Pro Pro Ala Lys Ala Ala Leu Leu Thr His
    50                  55                  60

Pro Leu Met Lys Asn Leu Pro Pro Glu Thr Leu Arg Leu Phe Phe Ile
65                  70                  75                  80

His Ser Ala Tyr Lys Phe Met Gly Asp Ile Ala Ile Phe Glu Thr Glu
                85                  90                  95

Thr Val Asn Glu Val Ala Met Lys Ile Ala Asn Gly His Thr Pro Ile
            100                 105                 110

Thr Phe Pro Asp Asp Ile Arg His Asp Ala Leu Thr Val Ile Ile Asp
        115                 120                 125

Glu Ala Tyr His Ala Tyr Val Ala Arg Asp Phe Met Arg Gln Ile Glu
    130                 135                 140

Gln Arg Thr Gly Val Lys Pro Leu Pro Leu Gly Thr Glu Thr Asp Leu
145                 150                 155                 160

Ser Arg Ala Met Ala Phe Gly Lys His Arg Leu Pro Glu Thr Leu His
                165                 170                 175

Gly Leu Trp Glu Ile Ile Ala Val Cys Ile Gly Glu Asn Thr Leu Thr
            180                 185                 190

Lys Asp Leu Leu Asn Leu Thr Gly Glu Lys Ser Phe Asn Glu Val Leu
        195                 200                 205

His Gln Val Met Glu Asp His Val Arg Asp Glu Gly Arg His Ala Val
    210                 215                 220

Leu Phe Met Asn Val Leu Lys Leu Val Trp Ser Glu Met Glu Glu Ser
225                 230                 235                 240

Ala Arg Leu Ala Ile Gly Gln Leu Leu Pro Glu Phe Ile Arg Glu Tyr
                245                 250                 255

Leu Ser Pro Lys Met Met Ala Glu Tyr Glu Arg Val Val Leu Glu Gln
            260                 265                 270

Leu Gly Leu Ala Ala Glu His Ile Glu Arg Ile Leu Ser Glu Thr Tyr
        275                 280                 285

Ser Glu Pro Pro Leu Glu Asp Phe Arg Ala Arg Tyr Pro Leu Ser Gly
    290                 295                 300

Tyr Leu Val Tyr Val Leu Met Gln Cys Asp Val Leu Ser His Ala Pro
305                 310                 315                 320

Thr Arg Glu Ala Phe Arg Arg Phe Lys Leu Leu Ala His
                325                 330


<210> SEQ ID NO 58
<211> LENGTH: 642
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(642)
<223> OTHER INFORMATION: CysS

<400> SEQUENCE: 58

Met Ala Asn Gln Arg Val Ala Phe Ile Glu Leu Thr Val Phe Ser Gly
1               5                   10                  15

Val Tyr Pro Leu Ala Ser Gly Tyr Met Arg Gly Val Ala Glu Gln Asn
            20                  25                  30

Pro Leu Ile Arg Glu Ser Cys Ser Phe Glu Ile His Ser Ile Cys Ile
        35                  40                  45

Asn Asp Asp Arg Phe Glu Asp Lys Leu Asn Lys Ile Asp Ala Asp Val
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    50                  55                  60

Tyr Ala Ile Ser Cys Tyr Val Trp Asn Met Gly Phe Val Lys Arg Trp
65                  70                  75                  80

Leu Pro Thr Leu Thr Ala Arg Lys Pro Asn Ala His Ile Ile Leu Gly
                85                  90                  95

Gly Pro Gln Val Met Asn His Gly Ala Gln Tyr Leu Asp Pro Gly Asn
            100                 105                 110

Glu Arg Val Val Leu Cys Asn Gly Glu Gly Glu Tyr Thr Phe Ala Asn
        115                 120                 125

Tyr Leu Ala Glu Leu Cys Ser Pro Gln Pro Asp Leu Gly Lys Val Lys
    130                 135                 140

Gly Leu Ser Phe Tyr Arg Asn Gly Glu Leu Ile Thr Thr Glu Pro Gln
145                 150                 155                 160

Ala Arg Ile Gln Asp Leu Asn Thr Val Pro Ser Pro Tyr Leu Glu Gly
                165                 170                 175

Tyr Phe Asp Ser Glu Lys Tyr Val Trp Ala Pro Leu Glu Thr Asn Arg
            180                 185                 190

Gly Cys Pro Tyr Gln Cys Thr Tyr Cys Phe Trp Gly Ala Ala Thr Asn
        195                 200                 205

Ser Arg Val Phe Lys Ser Asp Met Asp Arg Val Lys Ala Glu Ile Thr
    210                 215                 220

Trp Leu Ser Gln His Arg Ala Phe Tyr Ile Phe Ile Thr Asp Ala Asn
225                 230                 235                 240

Phe Gly Met Leu Thr Arg Asp Ile Glu Ile Ala Gln His Ile Ala Glu
                245                 250                 255

Cys Lys Arg Lys Tyr Gly Tyr Pro Leu Thr Ile Trp Leu Ser Ala Ala
            260                 265                 270

Lys Asn Ser Pro Asp Arg Val Thr Gln Ile Thr Arg Ile Leu Ser Gln
        275                 280                 285

Glu Gly Leu Ile Ser Thr Gln Pro Val Ser Leu Gln Thr Met Asp Ala
    290                 295                 300

Asn Thr Leu Lys Ser Val Lys Arg Gly Asn Ile Lys Glu Ser Ala Tyr
305                 310                 315                 320

Leu Ser Leu Gln Glu Glu Leu His Arg Ser Lys Leu Ser Ser Phe Val
                325                 330                 335

Glu Met Ile Trp Pro Leu Pro Gly Glu Thr Leu Glu Thr Phe Arg Glu
            340                 345                 350

Gly Ile Gly Lys Leu Cys Ser Tyr Asp Ala Asp Ala Ile Leu Ile His
        355                 360                 365

His Leu Leu Leu Ile Asn Asn Val Pro Met Asn Ser Gln Arg Glu Glu
    370                 375                 380

Phe Lys Leu Glu Val Ser Asn Asp Glu Asp Pro Asn Ser Glu Ala Gln
385                 390                 395                 400

Val Val Val Ala Thr Lys Asp Val Thr Arg Glu Glu Tyr Lys Glu Gly
                405                 410                 415

Val Arg Phe Gly Tyr His Leu Thr Ser Leu Tyr Ser Leu Arg Ala Leu
            420                 425                 430

Arg Phe Val Gly Arg Tyr Leu Asp Lys Gln Gly Arg Leu Ala Phe Lys
        435                 440                 445

Asp Leu Ile Ser Ser Phe Ser Glu Tyr Cys Lys Arg Asn Pro Asp His
    450                 455                 460
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Pro Tyr Thr Gln Tyr Ile Thr Ser Val Ile Asp Gly Thr Ser Gln Ser
465                 470                 475                 480

Lys Phe Ser Ala Asn Gly Gly Ile Phe His Val Thr Leu His Glu Phe
                485                 490                 495

Arg Arg Glu Phe Asp Gln Leu Leu Phe Gly Phe Ile Gln Thr Leu Gly
            500                 505                 510

Met Met Asn Asp Glu Leu Leu Glu Phe Leu Phe Glu Met Asp Leu Leu
        515                 520                 525

Asn Arg Pro His Val Tyr Ser Asn Thr Pro Ile Asn Asn Gly Glu Gly
    530                 535                 540

Leu Leu Lys His Val Thr Val Val Ser Lys Glu Lys Asp Ala Ile Val
545                 550                 555                 560

Leu Arg Val Pro Glu Lys Tyr Ala Gln Leu Thr Ser Glu Leu Leu Gly
                565                 570                 575

Leu Glu Gly Ala Pro Ser Thr Ser Leu Arg Val Lys Tyr Arg Gly Thr
            580                 585                 590

Gln Met Pro Phe Met Ala Asn Lys Pro Tyr Glu Asp Asn Leu Ser Tyr
        595                 600                 605

Cys Glu Ala Lys Leu His Lys Met Gly Ser Ile Leu Pro Val Trp Glu
    610                 615                 620

Ser Ala Val Pro Ser Arg Thr Pro Val Arg Arg Pro Gln Val Ala Val
625                 630                 635                 640

Ala Gly
```

<210> SEQ ID NO 59
<211> LENGTH: 1267
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1267)
<223> OTHER INFORMATION: CysT

<400> SEQUENCE: 59

```
Met His Arg Val Lys Pro Leu Ile Gly Pro Val Leu Ser Ala Leu Leu
1               5                   10                  15

Leu Cys Ala Leu Pro Ala Arg Ala Gln Ile Ala Ala Ala His Val Tyr
            20                  25                  30

His Asn His Met Pro Asn Phe Trp Ala Tyr Tyr Asp Leu Gly Gln Tyr
        35                  40                  45

Ala Ser Thr Pro Thr Gly Gly Pro Ile Arg Tyr Met Tyr Asp Ala Gln
    50                  55                  60

Val Ile Asn Leu Lys Lys Asn Pro Pro Ser Asn Tyr Thr Tyr Tyr Leu
65                  70                  75                  80

Pro Ser Gly Ala Pro Met Pro His Asp Asp Leu Val Thr Tyr Tyr Ser
                85                  90                  95

His Asn Ala Lys Thr Gly Ala Tyr Leu Tyr Trp Pro Pro Ser Val Ala
            100                 105                 110

Ser Asp Met Lys Thr Asn Ala Pro Thr Gly Gln Val His Val Thr Met
        115                 120                 125

Ser Gly Ala Val Val Asn Asn Val Gln Asp Leu Val Thr Leu Lys Asn
    130                 135                 140

Val Pro Gly Tyr Asp Asn Pro Asn Trp Gly Ala Ser Trp Lys Asp Arg
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145                 150                 155                 160

Tyr Ser Ala Leu Leu Thr Pro Ala Gly Asn Arg Thr Leu Asp Leu Ile
                165                 170                 175

His Phe Thr Gly His His Ser Met Gly Pro Leu Val Gly Pro Asp Tyr
            180                 185                 190

Phe Leu Lys Asp Leu Ile Tyr Gln Ser Ala Thr Leu Ala Gln Pro Tyr
        195                 200                 205

Phe Leu Gly Gly Ser Phe Gln Ser Ser Lys Gly Phe Phe Pro Thr Glu
    210                 215                 220

Leu Gly Phe Ser Glu Arg Leu Ile Pro Thr Leu Ser Lys Leu Gly Val
225                 230                 235                 240

Gln Trp Ala Val Ile Gly Asp Asn His Phe Ser Arg Thr Leu Lys Asp
                245                 250                 255

Tyr Pro Tyr Leu Asn Asp Pro Gly Ser Asp Thr Leu Val Ser Pro Pro
            260                 265                 270

Asn Arg Ala Asp Leu Gln Asn Thr Ser Ser Val Gly Ser Trp Val Ser
        275                 280                 285

Ala Gln Met Ala His Glu Gln Gln Val Ile Lys Asn Lys Tyr Pro Phe
    290                 295                 300

Ala Ser Thr Pro His Trp Val Arg Tyr Val Asp Pro Ala Thr Gly Ala
305                 310                 315                 320

Glu Ser Arg Val Val Gly Ile Pro Val Asn Gln Asn Gly Ser Trp Leu
                325                 330                 335

Glu Gly Trp Glu Gly Glu Ala Thr Val Asp Val Val Asn Leu Lys Ser
            340                 345                 350

Phe Glu Gly Leu Val Pro Gln Arg Gln Phe Phe Val Ile Ala His Asp
        355                 360                 365

Gly Asp Asn Ser Ser Gly Arg Ala Gly Ser Asp Ser Thr Trp Tyr Asn
    370                 375                 380

Gly Arg Ser Val Thr Cys Ala Asn Gly Val Gln Cys Val Gly Ile Ser
385                 390                 395                 400

Glu Tyr Leu Val His His Thr Pro Ala Ser Thr Asp Val Val His Val
                405                 410                 415

Gln Asp Gly Ser Trp Val Asp Thr Arg Asp Ser Ser Ser Asp Pro Gln
            420                 425                 430

Trp His His Trp Lys Leu Pro Phe Gly Ile Trp Lys Gly Gln Phe Pro
        435                 440                 445

Ala Phe Asn Ala Ala Thr Gly Leu Asn Leu Ser Pro Lys Thr Asn Leu
    450                 455                 460

Ser Gly Val Gln Glu Gly Met Thr Val Ser Leu Glu His Gly Trp His
465                 470                 475                 480

Tyr Leu Glu Arg Asn Phe Ala Leu Leu Gln Ala Ala Leu Asn Tyr Ala
                485                 490                 495

Lys Thr Ala Glu Gln Ile Trp Leu Asp Ala His Pro Asn His Trp Ser
            500                 505                 510

Pro Thr Thr Ala Ile Asp Lys Gln Ile Thr His Thr Gly Asn Gln Leu
        515                 520                 525

Asn Pro Trp Met Met Ser Phe Pro Val Lys Gly Asp Val Asn Asn Asp
    530                 535                 540

Trp Ala Gly Gly Ala Asn Pro Ala Glu Leu Ala Trp Tyr Phe Leu Leu
545                 550                 555                 560
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Pro Ala Met Asp Ser Gly Phe Gly Tyr Tyr Asp Glu Asn Gln Asp Asp
               565                 570                 575

Asn Val Lys Pro Thr Leu Ser Phe Asn Gln Ser Leu Tyr Phe Ser Lys
           580                 585                 590

Pro Tyr Val Gln Gln Arg Ile Ala Gln Asp Lys Thr Gly Pro Ser Val
       595                 600                 605

Trp Trp Ala Gln Arg Trp Pro Tyr Asn Pro Gly Ser Ala Asn Thr Asp
   610                 615                 620

Lys Ser Glu Gly Trp Thr Leu His Phe Phe Asn Asn His Phe Ala Leu
625                 630                 635                 640

Tyr Thr Tyr Ala Tyr Asp Ala Ser Gly Ile Ser Ser Ile Lys Ala Arg
               645                 650                 655

Val Arg Val His Thr His Lys Ser Ile Asp Pro Leu Asp Asn Thr His
           660                 665                 670

Lys Val Tyr Asp Pro Ala Ala Arg Lys Ala Ala Gly Val Pro Asn Ile
       675                 680                 685

Asp Pro Ala Arg Val Gly Ala Trp Val Asp Tyr Pro Leu Thr Arg Arg
   690                 695                 700

Asp Leu Lys Pro Val Met Asn Gly Val Ser Trp Gln Pro Ala Tyr Leu
705                 710                 715                 720

Pro Val Met Ala Lys Val Pro Ala Gln Glu Ile Gly Asp Leu Tyr Tyr
               725                 730                 735

Val Tyr Leu Gly Asn Tyr Arg Asp Gln Leu Leu Asp Tyr Tyr Ile Glu
           740                 745                 750

Ala Thr Asp Ser Arg Gly Asn Ile Thr Arg Gly Glu Ile Gln Ser Val
       755                 760                 765

Tyr Val Gly Ser Gly Arg Tyr Asn Leu Val Gly Gly Lys Tyr Ile Glu
   770                 775                 780

Asp Pro Asn Gly Thr Val Gln Gly Thr His Pro Phe Leu Val Val Asp
785                 790                 795                 800

Thr Thr Ala Pro Ser Val Pro Ser Gly Leu Thr Ala Lys Ala Lys Thr
               805                 810                 815

Asp Arg Ser Val Thr Leu Ser Trp Ser Ala Ala Ser Asp Asn Val Ala
           820                 825                 830

Val Ser Gly Tyr Asp Val Phe Arg Asp Gly Thr Gln Val Gly Ser Ser
       835                 840                 845

Thr Ser Thr Ala Tyr Thr Asp Ser Gly Leu Ser Pro Ser Thr Gln Tyr
   850                 855                 860

Ser Tyr Thr Val Arg Ala Arg Asp Ala Ala Gly Asn Ala Ser Ala Gln
865                 870                 875                 880

Ser Thr Ala Leu Ser Val Ala Thr Leu Thr Pro Asp Thr Thr Pro Pro
               885                 890                 895

Ser Val Pro Ser Gly Leu Thr Ala Ser Gly Thr Thr Ser Ser Ser Val
           900                 905                 910

Ala Leu Ala Trp Thr Ala Ser Thr Asp Asn Tyr Gly Val Ala Asn Tyr
       915                 920                 925

Glu Val Leu Arg Asn Gly Thr Gln Val Ala Ser Val Thr Gly Thr Thr
   930                 935                 940

Tyr Ser Asp Thr Gly Leu Ser Pro Ser Thr Thr Tyr Ser Tyr Thr Val
945                 950                 955                 960
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Arg Ala Arg Asp Ala Ala Gly Asn Val Ser Ser Pro Ser Thr Ala Leu
                965                 970                 975

Ser Val Thr Thr Gln Thr Gly Asn Ser Ala Thr Val Tyr Tyr Phe Asn
            980                 985                 990

Asn Asn Phe Ala Leu Lys Tyr Ile  His Phe Arg Ile Gly  Gly Gly Thr
        995                 1000                1005

Trp Thr  Thr Val Pro Gly Asn  Val Met Ala Thr Ser  Glu Val Pro
    1010                1015                1020

Gly Tyr  Ala Lys Tyr Thr Val  Asn Leu Gly Ala Ala  Thr Gln Leu
    1025                1030                1035

Glu Cys  Val Phe Asn Asp Gly  Lys Gly Thr Trp Asp  Asn Asn Lys
    1040                1045                1050

Gly Asn  Asn Tyr Leu Leu Pro  Ala Gly Thr Ser Thr  Val Lys Asp
    1055                1060                1065

Gly Val  Val Ser Ser Gly Ala  Pro Ala Leu Asp Thr  Thr Ala Pro
    1070                1075                1080

Ser Val  Pro Ser Gly Leu Thr  Ala Ala Ser Lys Thr  Ser Ser Ser
    1085                1090                1095

Val Ser  Leu Ser Trp Ser Ala  Ser Thr Asp Ala Ser  Gly Ile Ala
    1100                1105                1110

Gly Tyr  Asp Val Tyr Arg Asp  Gly Ser Leu Val Gly  Ser Pro Val
    1115                1120                1125

Ser Thr  Ser Tyr Thr Asp Ser  Asp Leu Ser Ala Gly  Thr Thr Tyr
    1130                1135                1140

Arg Tyr  Thr Val Arg Ala Arg  Asp Thr Ala Gly Asn  Ala Ser Ala
    1145                1150                1155

Gln Ser  Thr Ala Leu Ser Val  Thr Thr Ser Thr Ser  Ser Ala Thr
    1160                1165                1170

Ser Val  Thr Phe Asn Val Thr  Ala Ser Thr Val Val  Gly Gln Asn
    1175                1180                1185

Val Tyr  Leu Val Gly Asn His  Ala Ala Leu Gly Asn  Trp Asn Thr
    1190                1195                1200

Gly Ala  Ala Ile Leu Leu Ser  Pro Ala Ser Tyr Pro  Lys Trp Ser
    1205                1210                1215

Val Thr  Leu Ser Leu Pro Gly  Ser Thr Ala Leu Glu  Tyr Lys Tyr
    1220                1225                1230

Ile Lys  Lys Asp Gly Ser Gly  Asn Val Thr Trp Glu  Ser Gly Ala
    1235                1240                1245

Asn Arg  Ser Thr Thr Ile Pro  Ala Ser Gly Thr Ala  Thr Leu Asn
    1250                1255                1260

Asp Thr  Trp Lys
    1265


<210> SEQ ID NO 60
<211> LENGTH: 276
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(276)
<223> OTHER INFORMATION: ORF1

<400> SEQUENCE: 60

Val Pro His Pro Ser Glu Gln Ser Ala Pro Ser Gly Leu Arg Ala Arg
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1               5                   10                  15

Leu His Glu Ile Ile Phe Glu Ser Asp Thr Pro Ala Gly Arg Ala Phe
            20                  25                  30

Asp Val Ala Leu Leu Trp Ala Ile Val Leu Ser Val Leu Ala Val Met
        35                  40                  45

Leu Glu Ser Val Glu Ser Ile Ser Val Gln His Gly Gln Thr Ile Arg
    50                  55                  60

Val Leu Glu Trp Cys Phe Thr Gly Leu Phe Thr Leu Glu Tyr Val Leu
65                  70                  75                  80

Arg Leu Leu Ser Val Lys Arg Pro Leu Arg Tyr Ala Leu Ser Phe Phe
                85                  90                  95

Gly Leu Val Asp Leu Leu Ala Ile Leu Pro Ser Val Leu Ser Leu Met
            100                 105                 110

Leu Pro Gly Met Gln Ser Leu Leu Val Val Arg Val Phe Arg Leu Leu
        115                 120                 125

Arg Val Phe Arg Val Leu Lys Leu Ala Ser Phe Leu Gly Glu Ala Asp
    130                 135                 140

Val Leu Leu Thr Ala Leu Arg Ala Ser Arg Arg Lys Ile Ile Val Phe
145                 150                 155                 160

Leu Gly Ala Val Leu Ser Thr Val Val Ile Met Gly Ala Val Met Tyr
                165                 170                 175

Met Val Glu Gly Arg Ala Asn Gly Phe Asp Ser Ile Pro Arg Gly Met
            180                 185                 190

Tyr Trp Ala Ile Val Thr Met Thr Thr Val Gly Tyr Gly Asp Leu Ser
        195                 200                 205

Pro Lys Thr Val Pro Gly Gln Phe Ile Ala Ser Val Leu Met Ile Met
    210                 215                 220

Gly Tyr Gly Ile Leu Ala Val Pro Thr Gly Ile Val Ser Val Glu Leu
225                 230                 235                 240

Ala Gln Ala Thr Arg Gln His Ala Ile Asp Pro Arg Ala Cys Pro Gly
                245                 250                 255

Cys Gly Leu Gln Gly His Asp Leu Asp Ala His His Cys Lys His Cys
            260                 265                 270

Gly Thr Ala Leu
        275


<210> SEQ ID NO 61
<211> LENGTH: 78
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(78)
<223> OTHER INFORMATION: ORF2

<400> SEQUENCE: 61

Met Ala Gln Asp Gln Asp Arg Glu Lys Leu His Ser Asp Ala Asp Lys
1               5                   10                  15

Glu Arg Leu His Pro Lys Val Asp Ser Gly Asp Val Ser Gly Arg Gly
            20                  25                  30

Arg Glu Arg Arg Pro Asp Glu Glu Tyr Pro Lys Gln Arg Asn Ala Gly
        35                  40                  45

Glu Phe Gly Thr His Gly Gly Pro Asn Lys Gly Gly Lys Glu Asp Arg
    50                  55                  60
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Arg Gln Leu His Ala Pro Gly Ser Ser Lys Ala Gly Ser Gln
65 70 75

<210> SEQ ID NO 62
<211> LENGTH: 162
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(162)
<223> OTHER INFORMATION: ORF3

<400> SEQUENCE: 62

Met Gly Arg Thr Tyr Ser Phe Glu Pro Phe Leu Ser Gln Gln Pro Ala
1 5 10 15

Gln Thr Tyr Lys Gly Ser Gly Pro Arg Leu Gly Asn Glu Glu His Lys
20 25 30

Ile Ala Leu Thr Lys Glu Glu Glu Lys Ala Ala Leu Pro Asp Thr Pro
35 40 45

Thr Gly Tyr Gly Gln Ala His Ala Glu Thr Val Lys Arg Tyr Arg Ala
50 55 60

Arg Ala Glu Lys Lys Arg Thr Glu Pro Lys Thr Pro Ala Thr Arg Ala
65 70 75 80

Lys Lys Ala Ala Pro Lys Ala Lys Pro Thr Arg Lys Val Ala Thr Gln
85 90 95

Glu Ala Thr Ala Lys Ala Pro Thr Arg Gln Ala Arg Glu Glu Thr Glu
100 105 110

Pro Lys Ala Pro Ala Arg Lys Lys Leu Ser Ala Thr Gly Leu Val Gly
115 120 125

Ser Ile Gly Arg Lys Val Val Thr Arg Ala Ala Val Ala Ala Lys Lys
130 135 140

Thr Val Ala Arg Ala Val Lys Thr Ala Ala Ala Arg Lys Ser Ala Lys
145 150 155 160

Lys Arg

<210> SEQ ID NO 63
<211> LENGTH: 87
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(87)
<223> OTHER INFORMATION: ORF4

<400> SEQUENCE: 63

Met Ser Pro Ala Arg Arg Lys Glu Ser Lys Gln His Glu Val Gly Ser
1 5 10 15

Ala Thr His Ala Arg Arg Val Ile Val Ala Thr Asp Gly Arg Gly Trp
20 25 30

Tyr Val Arg Phe Glu Gly Asn Arg Gln Leu Gly Arg Tyr Ser Asn Val
35 40 45

Thr Gln Ala Ile His Gly Gly Arg Arg Leu Ala Arg Gln His Lys Pro
50 55 60

Ala Gly Leu Val Val Arg Tyr Leu Asp Gly Glu Glu Glu Glu Ser Trp
65 70 75 80

Tyr Gly Asp Arg Glu Ala Pro

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85

<210> SEQ ID NO 64
<211> LENGTH: 149
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(149)
<223> OTHER INFORMATION: ORF5

<400> SEQUENCE: 64

Met Lys His Ile Lys Ala Val Val Val Gly Ala Leu Ser Ala Ala Leu
1 5 10 15

Leu Phe Gly Val Gly Cys Gln Thr Thr Gly Gly Ala Gly Asn Gln Gly
20 25 30

Thr Gly Gly Ser Asp Thr Ser Gln Gly Gly Thr Met Thr Gly Ser Glu
35 40 45

Thr Thr Gly Thr Gly Thr Thr Gly Gly Thr Thr Glu Gly Gly Asp Thr
50 55 60

Thr Gly Gly Gly Thr Gly Gly Thr Gly Ala Gly Asp Ile Asp Gly Ser
65 70 75 80

Ser Ser Gly Ser Thr Gly Ser Gly Ser Asp Val Gly Gly Ser Gly Gly
85 90 95

Ser Gly Val Ser Ser Glu Pro Gly Gly Phe Ser Pro Asp Ala Ser Gly
100 105 110

Val Asp Ser Asp Leu Gly Gly Ser Gly Thr Gly Ser Asp Val Asp Gly
115 120 125

Ser Gly Ser Thr Asp Ser Ser Gly Asn Met Ser Gly Thr Gly Ser Glu
130 135 140

Asp Asp Thr Ser Arg
145

<210> SEQ ID NO 65
<211> LENGTH: 525
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(525)
<223> OTHER INFORMATION: ORF6

<400> SEQUENCE: 65

Met Ser Thr Arg Thr Ser Leu Ala Leu Ala Ala Ser Leu Ala Ala Leu
1 5 10 15

Pro Ala Leu Ala Gln Glu Arg Pro Ser Glu Gly Asp Leu Phe Gly Gly
20 25 30

Asp Thr Pro Glu Thr Lys Pro Ala Pro Ala Asp Ala Pro Arg Pro Asp
35 40 45

Glu Ser Ser Leu Phe Gly Asp Thr Pro Ala Ser Thr Pro Ala Ala Gln
50 55 60

Ser Ala Ala Ala Thr Ala Ala Pro Asp Lys Pro Ser Ala Thr Pro Gln
65 70 75 80

Asp Arg Asp Ala Gln Ala Leu Gly Gly Pro Ser Ala Thr Asn Ala Phe
85 90 95

Asp Thr Glu Glu Ala Val Glu Asp Pro Leu Lys Ile Gly Gly Arg Phe
100 105 110

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Tyr Leu Arg Ala Tyr Ser Gln Ala Asn Glu Gly Val Ser Phe Ser Asn
        115                 120                 125

Thr Thr Phe Ser Ala Pro Met Leu Val Asp Gly Tyr Phe Asp Ala Arg
    130                 135                 140

Pro Thr Glu Arg Leu Arg Gly Phe Val Leu Gly Arg Leu Thr Phe Asp
145                 150                 155                 160

Pro Thr Arg Lys Ala Gly Ser Leu Gly Ile Val Pro Thr Ser Thr Ser
                165                 170                 175

Thr Ser Asn Val Ala Ala Asp Pro Val Val Leu Leu Asp Gln Ala Trp
            180                 185                 190

Leu Arg Phe Asp Leu Asp His Lys Leu Phe Ile Thr Val Gly Lys Gln
        195                 200                 205

His Val Lys Trp Gly Thr Ser Arg Phe Trp Asn Pro Thr Asp Phe Leu
    210                 215                 220

Ser Pro Gln Arg Arg Asp Pro Leu Ala Leu Leu Asp Thr Arg Thr Gly
225                 230                 235                 240

Ala Thr Met Leu Lys Met His Met Pro Trp Glu Ala Lys Gly Trp Asn
                245                 250                 255

Phe Tyr Val Leu Gly Leu Leu Asp Asn Ala Gly Pro Ala Asn Thr Leu
            260                 265                 270

Gly Arg Val Gly Gly Ala Ala Arg Ala Glu Val Val Leu Gly His Thr
        275                 280                 285

Glu Leu Gly Val Asp Ala Val Leu Gln His Gly Arg Lys Pro Arg Phe
    290                 295                 300

Gly Leu Asp Leu Ser Ser Gly Leu Gly Pro Ile Asp Ile Tyr Gly Glu
305                 310                 315                 320

Leu Ala Leu Lys Lys Gly Ser Asp Ala Pro Met Phe Arg Met Pro Gln
                325                 330                 335

Gly Val Ser Leu Gly Asp Leu Leu Gly Gln Phe Gln Gly Asn Gly Gly
            340                 345                 350

Met Pro Pro Asp Leu Gly Ala Leu Pro Ile Glu Ala Tyr Tyr Pro Glu
        355                 360                 365

Gly Tyr Thr Pro Gln Val Ser Gly Gly Ala Thr Trp Thr Phe Ala Tyr
    370                 375                 380

Ser Glu Ser Asp Thr Ala Thr Val Gly Val Glu Tyr Phe Tyr Asn Ser
385                 390                 395                 400

Met Gly Tyr Pro Gly Ser Leu Ala Tyr Pro Tyr Leu Ile Leu Gln Gly
                405                 410                 415

Gln Tyr Gln Pro Phe Tyr Leu Gly Arg His Tyr Ala Ala Val Tyr Ala
            420                 425                 430

Phe Leu Ser Gly Pro Gly Ser Trp Asp Asn Thr Asn Phe Ile Leu Ser
        435                 440                 445

Asn Leu Gly Asn Leu Ser Asp Arg Ser Phe Ile Thr Arg Leu Asp Val
    450                 455                 460

Thr His Arg Ala Leu Arg Tyr Leu Ser Ile Glu Ala Phe Ile Ala Ala
465                 470                 475                 480

Asn Tyr Gly Gln Arg Gly Gly Glu Phe Arg Phe Ala Leu Asn Leu Pro
                485                 490                 495

Ala Leu Arg Met Gly Glu Gln Val Thr Pro Pro Ile Ala Val Ala Pro
            500                 505                 510
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Pro Thr Ile Gln Ala Gly Val Gly Leu Arg Ile Asp Leu
        515                 520                 525


<210> SEQ ID NO 66
<211> LENGTH: 261
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(261)
<223> OTHER INFORMATION: ORF7

<400> SEQUENCE: 66

Met Thr Leu Arg Asn Leu Leu Gly Ala Leu Phe Ala Ala Leu Leu Leu
1               5                   10                  15

Ala Ala Pro Thr Ala Arg Ala Asp Leu Thr Asp Pro Ala Glu Ile Lys
            20                  25                  30

Lys Leu Leu Glu Thr Leu Asp Asn Arg Gln Arg Asn Gly Gly Asp Tyr
        35                  40                  45

Lys Ser Leu Val Tyr Ile Glu Gln Lys Glu Lys Asp Lys Thr Asp Val
    50                  55                  60

Val Arg Glu Ala Val Val Tyr Arg Arg Asp Glu Lys Asp Gln Leu Met
65                  70                  75                  80

Ile Leu Met Thr Lys Pro Lys Gly Glu Ala Gly Lys Gly Tyr Leu Arg
                85                  90                  95

Leu Asp Lys Asn Leu Trp Ser Tyr Asp Pro Asn Thr Gly Lys Trp Asp
            100                 105                 110

Arg Arg Thr Glu Arg Glu Arg Ile Ala Gly Thr Asp Ser Arg Arg Ala
        115                 120                 125

Asp Phe Asp Glu Ser Arg Leu Ala Glu Glu Leu Asp Gly Lys Phe Glu
    130                 135                 140

Gly Glu Glu Lys Leu Gly Lys Phe Thr Thr Trp Lys Leu Val Leu Thr
145                 150                 155                 160

Ala Lys Pro Asn Val Asp Val Ala Tyr Pro Val Val His Leu Trp Val
                165                 170                 175

Glu Lys Asp Thr Asn Asn Ile Leu Lys Arg Gln Glu Phe Ala Leu Ser
            180                 185                 190

Gly Arg Leu Met Arg Thr Ser Tyr Phe Pro Lys Trp Met Lys Leu Phe
        195                 200                 205

Ser Glu Ser Lys Lys Ala Asp Val Trp Tyr Pro Gln Glu Met Arg Phe
    210                 215                 220

Tyr Asp Glu Val Glu Lys Thr Asn Ser Thr Val Ile Val Val Lys Ser
225                 230                 235                 240

Val Asp Leu Arg Ser Leu Glu Glu Asn Ile Phe Thr Lys Ala Trp Phe
                245                 250                 255

Glu Ser Lys Ser Arg
            260


<210> SEQ ID NO 67
<211> LENGTH: 433
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(433)
<223> OTHER INFORMATION: ORF8
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<400> SEQUENCE: 67

```
Met Gln Gln Leu Leu Leu Ile Ala Val Arg Asn Leu Gly Thr His Lys
1               5                   10                  15

Arg Arg Thr Leu Leu Leu Gly Gly Ala Ile Ala Gly Val Thr Ala Leu
            20                  25                  30

Leu Val Ile Leu Met Gly Leu Ser Asn Gly Met Lys Asp Thr Met Leu
        35                  40                  45

Arg Ser Ala Thr Thr Leu Val Thr Gly His Val Asn Val Ala Gly Phe
    50                  55                  60

Tyr Lys Val Thr Ala Gly Gln Ser Ala Pro Val Val Thr Ser Tyr Pro
65                  70                  75                  80

Lys Leu Leu Glu Gln Leu Arg Lys Glu Val Pro Glu Leu Asp Phe Ser
                85                  90                  95

Val Gln Arg Thr Arg Gly Trp Val Lys Leu Val Ser Glu Ser Gly Ser
            100                 105                 110

Val Gln Thr Gly Ile Gly Gly Ile Asp Val Ala Ala Glu Thr Gly Ile
        115                 120                 125

Arg Lys Val Leu Gln Leu Arg Glu Gly Arg Leu Glu Asp Leu Ala Gln
    130                 135                 140

Pro Asn Thr Leu Leu Leu Phe Asp Glu Gln Ala Lys Arg Leu Glu Val
145                 150                 155                 160

Lys Val Gly Asp Ser Val Thr Leu Ser Ala Ser Thr Met Arg Gly Ile
                165                 170                 175

Ser Asn Thr Val Asp Val Arg Val Val Ala Ile Ala Ala Asn Val Gly
            180                 185                 190

Met Leu Ser Ser Phe Asn Val Leu Val Pro Asn Ala Thr Leu Arg Ala
        195                 200                 205

Leu Tyr Gln Leu Arg Glu Asp Ser Thr Gly Ala Leu Met Leu His Leu
    210                 215                 220

Lys Asp Met Ser Ala Ile Pro Ser Val Gln Ala Arg Leu Tyr Lys Arg
225                 230                 235                 240

Leu Pro Glu Leu Gly Tyr Gln Val Leu Glu His Asp Pro Arg Ala Phe
                245                 250                 255

Phe Met Lys Phe Gln Thr Val Asn Arg Glu Ala Trp Thr Gly Gln Lys
            260                 265                 270

Leu Asp Ile Thr Asn Trp Glu Asp Glu Ile Ser Phe Ile Lys Trp Thr
        275                 280                 285

Val Ser Ala Met Asp Ala Leu Thr Gly Val Leu Ile Phe Val Leu Leu
    290                 295                 300

Ile Ile Ile Ala Val Gly Ile Met Asn Thr Leu Trp Ile Ala Ile Arg
305                 310                 315                 320

Glu Arg Thr Arg Glu Ile Gly Thr Leu Arg Ala Ile Gly Met Gln Arg
                325                 330                 335

Trp Tyr Val Leu Val Met Phe Leu Leu Glu Ala Leu Val Leu Gly Leu
            340                 345                 350

Leu Gly Thr Thr Val Gly Ala Leu Val Gly Met Gly Val Cys Leu Leu
        355                 360                 365

Ile Asn Ala Val Asp Pro Ser Val Pro Val Pro Val Gln Leu Phe Ile
    370                 375                 380

Leu Ser Asp Lys Leu His Leu Ile Val Lys Pro Gly Ser Val Met Arg
385                 390                 395                 400
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```
Ala Ile Ala Phe Ile Thr Leu Cys Thr Thr Phe Ile Ser Leu Ile Pro
                405                 410                 415

Ser Phe Leu Ala Ala Arg Met Lys Pro Ile Thr Ala Met His His Ile
            420                 425                 430

Gly


<210> SEQ ID NO 68
<211> LENGTH: 701
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(701)
<223> OTHER INFORMATION: ORF9

<400> SEQUENCE: 68

Met Gly Gln Leu Lys Leu Leu Leu Gln Val Ala Leu Arg Asn Leu Phe
1               5                   10                  15

Val Ser Arg Ile Asn Leu Leu Ile Gly Gly Ile Ile Phe Phe Gly Thr
            20                  25                  30

Val Leu Val Val Val Gly Gly Ser Leu Val Asp Ser Val Asp Glu Ala
        35                  40                  45

Met Ser Arg Ser Ile Ile Gly Ser Val Ala Gly His Leu Gln Val Tyr
    50                  55                  60

Ser Ala His Ser Lys Asp Glu Leu Ser Leu Phe Gly Gln Met Gly Arg
65                  70                  75                  80

Glu Pro Asp Leu Ser Ala Leu Asp Asp Phe Ser Arg Ile Lys Gln Leu
                85                  90                  95

Val Gln Gln His Pro Asn Val Lys Thr Val Val Pro Met Gly Thr Gly
            100                 105                 110

Ala Thr Phe Ile Asn Ser Gly Asn Thr Ile Asp Leu Thr Leu Ala Arg
        115                 120                 125

Leu Arg Asp Leu Tyr Lys Lys Ala Ala Gln Gly Asp Thr Pro Glu Leu
    130                 135                 140

Arg Gly Gln Ile His Ser Leu Gln Ala His Val Arg His Ile Ile Thr
145                 150                 155                 160

Leu Leu Glu Glu Asp Met Lys Arg Arg Arg Glu Ile Ile Asp Asp Lys
                165                 170                 175

Thr Thr Asp Pro Ala Asp Ala Glu Ala Met Ala Arg Ala Arg Ser Glu
            180                 185                 190

Ala Phe Trp Ala Asp Phe Asp Glu Lys Pro Phe Asp Ser Leu Glu Phe
        195                 200                 205

Leu Glu Asn Arg Ile Ala Pro Tyr Met Thr Asp Gly Asp Met Leu Ser
    210                 215                 220

Leu Arg Tyr Val Gly Thr Asp Leu Val Asn Phe Gln Lys Thr Phe Asp
225                 230                 235                 240

Arg Met Arg Ile Val Glu Gly Thr Pro Val Pro Pro Gly His Arg Gly
                245                 250                 255

Met Met Leu Ser Lys Phe Thr Tyr Glu Asn Asp Phe Lys Leu Lys Thr
            260                 265                 270

Ala His Arg Leu Asp Leu Ile Lys Glu Ala Arg Asp Thr Asn His Lys
        275                 280                 285

Thr Ile Ala Met Asp Pro Gln Leu Gln Arg Trp Val Lys Glu Asn Gln
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    290                 295                 300

Thr Gln Thr Arg Glu Ile Leu Phe Gln Leu Asp Asp Leu Lys Thr Lys
305                 310                 315                 320

Gln Ala Val Glu Arg Leu Gln Arg Val Leu Gly Ser Gln Glu Thr Asp
                325                 330                 335

Leu Gly Lys Leu Leu Pro Ala Phe Phe Thr Met Asp Asp Ala Asn Phe
            340                 345                 350

Asp Thr Arg Tyr Gln Gln Phe Tyr Ser Glu Leu Ala Thr Leu Leu Asp
        355                 360                 365

Leu Tyr Arg Ile Arg Ile Gly Asp Asp Leu Thr Ile Thr Ala Phe Ser
    370                 375                 380

Arg Thr Gly Tyr Val Gln Ser Val Asn Val Lys Ile Tyr Gly Thr Tyr
385                 390                 395                 400

Gln Phe Asp Gly Leu Glu Lys Ser Ala Val Ala Gly Ala Leu Asn Leu
                405                 410                 415

Leu Asp Leu Met Ser Phe Arg Glu Leu Tyr Gly Tyr Leu Thr Ala Glu
            420                 425                 430

Lys Lys Ala Glu Leu Ala Gly Leu Gln Lys Ala Ser Gly Val Gln Gln
        435                 440                 445

Val Lys Arg Glu Asp Ala Glu Thr Ala Leu Phe Gly Glu Gln Gly Ser
    450                 455                 460

Ala Ser Leu Val Ala Glu Gly Thr Ala Gly Gln Ile Asp Glu Asp Lys
465                 470                 475                 480

Gln Leu Asp Gly Leu Ala Gln Lys Leu His Arg Glu Glu Leu Ala Ser
                485                 490                 495

Arg Val Tyr Thr Gln Gln Glu Ile Glu Ser Gly Val Val Leu Ser Thr
            500                 505                 510

Ala Val Leu Leu Lys His Pro Glu Lys Leu Glu Gln Thr Leu Ala Glu
        515                 520                 525

Leu Arg Lys Ser Ala Asp Asp Ala Lys Leu Pro Leu Arg Ile Ile Ser
    530                 535                 540

Trp Gln Lys Ala Ser Gly Thr Ile Gly Gln Phe Val Leu Val Ala Lys
545                 550                 555                 560

Leu Val Leu Tyr Phe Ala Val Phe Ile Ile Phe Val Val Ala Leu Val
                565                 570                 575

Ile Ile Asn Asn Ala Met Met Met Ala Thr Leu Gln Arg Val Arg Glu
            580                 585                 590

Val Gly Thr Leu Arg Ala Ile Gly Ala Gln Arg Ser Phe Val Leu Ser
        595                 600                 605

Met Val Leu Val Glu Thr Val Val Leu Gly Leu Val Phe Gly Val Leu
    610                 615                 620

Gly Ala Ala Met Gly Gly Ala Ile Met Asn Met Leu Gly His Val Gly
625                 630                 635                 640

Ile Pro Ala Gly Asn Glu Ala Leu Tyr Phe Phe Phe Ser Gly Pro Arg
                645                 650                 655

Leu Phe Pro Ser Leu His Leu Ser Asn Leu Val Ala Ala Phe Val Ile
            660                 665                 670

Val Leu Val Val Ser Ala Leu Ser Thr Phe Tyr Pro Ala Tyr Leu Ala
        675                 680                 685

Thr Arg Val Ser Pro Leu Gln Ala Met Gln Thr Asp Glu
    690                 695                 700
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<210> SEQ ID NO 69
<211> LENGTH: 253
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(253)
<223> OTHER INFORMATION: ORF10

<400> SEQUENCE: 69

Met Ser Gln Val Thr Ala Leu Pro Gly Ser Thr Gln Pro Ile Val Ser
1 5 10 15

Leu Thr Glu Val Thr Lys Thr Tyr Ser Leu Gly Lys Val Gln Val Pro
20 25 30

Ala Leu Arg Gly Val Thr Leu Glu Val Tyr Pro Gly Glu Phe Ile Ser
35 40 45

Ile Ala Gly Pro Ser Gly Ser Gly Lys Thr Thr Ala Leu Asn Leu Ile
50 55 60

Gly Cys Val Asp Thr Ala Ser Ser Gly Val Val Ser Val Asp Gly Gln
65 70 75 80

Asp Thr Lys Lys Leu Thr Glu Arg Gln Leu Thr His Leu Arg Leu His
85 90 95

Thr Ile Gly Phe Ile Phe Gln Ser Phe Asn Leu Val Ser Val Leu Ser
100 105 110

Val Phe Gln Asn Val Glu Phe Pro Leu Leu Leu Gln Arg Lys Leu Asn
115 120 125

Ala Ser Glu Arg Arg Thr Arg Val Met Thr Leu Leu Glu Gln Val Gly
130 135 140

Leu Glu Lys His Ala Lys His Arg Pro Asn Glu Leu Ser Gly Gly Gln
145 150 155 160

Arg Gln Arg Val Ala Val Ala Arg Ala Leu Val Thr Arg Pro Lys Leu
165 170 175

Val Leu Ala Asp Glu Pro Thr Ala Asn Leu Asp Ser Val Thr Gly Gln
180 185 190

Asn Ile Ile Asp Leu Met Lys Glu Leu Asn Arg Lys Glu Gly Thr Thr
195 200 205

Phe Ile Phe Ser Thr His Asp Ala Lys Val Met Thr His Ala Asn Ala
210 215 220

Val Val Arg Leu Ala Asp Gly Lys Ile Leu Asp Arg Ile Thr Pro Ala
225 230 235 240

Glu Ala Gln Lys Val Met Ala Val Ser Glu Gly Gly His
245 250

<210> SEQ ID NO 70
<211> LENGTH: 397
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(397)
<223> OTHER INFORMATION: ORF11

<400> SEQUENCE: 70

Met Pro Gln Lys Phe Val Gly Lys Trp Lys Gly Gly Arg Val Lys Leu
1 5 10 15

-continued

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Val Asp Gly Arg Lys Val Trp Leu Leu Glu Lys Met Val Ser Gly Ala
            20                  25                  30

Arg Phe Ser Val Ser Leu Ala Val Ser Asn Glu Glu Asp Ala Leu Ala
        35                  40                  45

Glu Leu Ala Leu Phe Arg Arg Asp Arg Asp Ala Tyr Leu Ala Lys Val
    50                  55                  60

Lys Ala Asp Arg Ser Glu Glu Val Gln Ala Ser Thr Val Ala Gly Ala
65                  70                  75                  80

Val Pro Leu Ser Gly Asp Val Gly Pro Arg Leu Asp Ala Asp Ser Val
                85                  90                  95

Arg Glu Phe Leu Arg His Leu Thr Gln Arg Gly Arg Thr Glu Gly Tyr
            100                 105                 110

Arg Arg Asp Ala Arg Thr Tyr Leu Ser Gln Trp Ala Glu Val Leu Ala
        115                 120                 125

Gly Arg Asp Leu Ser Thr Val Ser Leu Leu Glu Leu Arg Arg Ala Leu
    130                 135                 140

Ser Gln Trp Pro Thr Ala Arg Lys Met Arg Ile Ile Thr Leu Lys Ser
145                 150                 155                 160

Phe Phe Ser Trp Leu Arg Glu Glu Asp Arg Leu Lys Ala Ala Glu Asp
                165                 170                 175

Pro Thr Leu Ser Leu Lys Val Pro Pro Ala Val Ala Glu Lys Gly Arg
            180                 185                 190

Arg Ala Lys Gly Tyr Ser Met Ala Gln Val Glu Lys Leu Tyr Ala Ala
        195                 200                 205

Ile Gly Ser Gln Thr Val Arg Asp Val Leu Cys Leu Arg Ala Lys Thr
    210                 215                 220

Gly Met His Asp Ser Glu Ile Ala Arg Leu Ala Ser Gly Lys Gly Glu
225                 230                 235                 240

Leu Arg Val Val Asn Asp Pro Ser Gly Ile Ala Gly Thr Ala Arg Phe
                245                 250                 255

Leu His Lys Asn Gly Arg Val His Ile Leu Ser Leu Asp Ala Gln Ala
            260                 265                 270

Leu Ala Ala Ala Gln Arg Leu Gln Val Arg Gly Arg Ala Pro Ile Arg
        275                 280                 285

Asn Thr Val Arg Glu Ser Ile Gly Tyr Ala Ser Ala Arg Ile Gly Gln
    290                 295                 300

Ser Pro Ile His Pro Ser Glu Leu Arg His Ser Phe Thr Thr Trp Ala
305                 310                 315                 320

Thr Asn Glu Gly Gln Val Val Arg Ala Thr Arg Gly Gly Val Pro Leu
                325                 330                 335

Asp Val Val Ala Ser Val Leu Gly His Gln Ser Thr Arg Ala Thr Lys
            340                 345                 350

Lys Phe Tyr Asp Gly Thr Glu Ile Pro Pro Met Ile Thr Val Pro Leu
        355                 360                 365

Lys Leu His His Pro Gln Asp Pro Ala Val Met Gln Leu Arg Arg Asn
    370                 375                 380

Cys Ser Pro Asp Pro Val Val Thr Arg Glu Ala Glu Ala
385                 390                 395


<210> SEQ ID NO 71
<211> LENGTH: 124
<212> TYPE: PRT
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<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(124)
<223> OTHER INFORMATION: ORF12

<400> SEQUENCE: 71

Val Leu Leu Ala Phe Pro Ser Gly Leu Leu Ser Leu Ala Leu Leu Ser
1 5 10 15

Thr Thr Thr Glu Ile Ser Ala Ala Leu Pro Val Asp Glu Cys Glu Ser
20 25 30

Ala Ser Leu Arg Ile Glu Leu Pro Ala Thr Pro Gly Gly Lys Pro Pro
35 40 45

Val Val Cys Leu Gly Pro Gly Leu Pro Ile His Phe Arg Phe Asp Ser
50 55 60

Ala Leu Gln Gln Lys Ser Leu Arg Ile Gln Asp Arg Gly Trp Phe Glu
65 70 75 80

Asp Trp Ala Leu Gly Gln Gln Thr Leu Val Leu Thr Pro His Asp Asn
85 90 95

Leu Val Ala Gly Lys Arg Ser Glu Val Glu Val Cys Phe Ala Asp Gly
100 105 110

Ala Ala Pro Ala Cys Ala Ser Phe Val Leu Arg Arg
115 120

<210> SEQ ID NO 72
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(112)
<223> OTHER INFORMATION: ORF13

<400> SEQUENCE: 72

Met His Thr Lys Val Pro Ser Val Phe Glu Ala Thr Pro Glu Ser Leu
1 5 10 15

Ser Asp Val Asp Tyr Gln Phe Trp His Glu Asp Phe Pro Arg Val Phe
20 25 30

Glu Arg Gln His Ile Asp Ala His Ala Val Pro Ala Ile Gly Ala Tyr
35 40 45

Leu Gly Glu Val Leu Val Arg Asn Leu Gly Gly Lys Trp Ile Pro Arg
50 55 60

Gln Lys Leu Asp Glu Ala Gln Val Leu Val Gly Asn Arg Val Trp Leu
65 70 75 80

Pro Phe Ala Arg Ala His His Tyr Met Arg Ser Cys Glu Ser Leu Leu
85 90 95

Asp Tyr Ser Leu Thr Gln Leu Tyr Arg Val Ala Glu Arg Tyr Arg Gly
100 105 110

<210> SEQ ID NO 73
<211> LENGTH: 304
<212> TYPE: PRT
<213> ORGANISM: Cystobacter velatus
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(304)
<223> OTHER INFORMATION: ORF 14

<400> SEQUENCE: 73

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Met Lys Val Leu Gly Leu Gly Asp Val Lys Ser Glu Asp Ser Leu Arg
1               5                  10                  15

Leu Thr Phe Glu Gly Ala Leu Asp Pro Gln Ala Ala Leu Glu Lys Val
            20                  25                  30

Leu Glu Pro Phe Phe Gln Ala Leu Glu Glu Tyr Ala Gly Asp Trp Met
        35                  40                  45

Pro Glu Val Val Ser Gly Arg Arg Arg Leu Lys Tyr Ser Arg Ala Asn
    50                  55                  60

Ile Trp Lys Ala Leu Glu Glu Arg Arg Asp Glu Arg Ser Thr Asp Thr
65                  70                  75                  80

Trp Leu Tyr Arg Thr Gln Arg Pro Thr Leu Glu Met Ser Leu His Leu
                85                  90                  95

Trp Phe Pro Pro Leu Pro Pro Ala Leu Asp Val Met Thr Thr Val Gln
            100                 105                 110

Pro Leu Thr Arg Phe Ala Glu Lys Glu Arg Cys Arg Gln Phe Val Glu
        115                 120                 125

Met Val Arg Thr Trp Ala Ser Cys Tyr Pro Val Thr His Ala Ala Ala
    130                 135                 140

His Ser Val Ala Asp Arg Ala Leu Ala Gly Ala Pro Asp Phe Gly Arg
145                 150                 155                 160

Asp Ala Arg Thr Ala Arg Arg Asp Gly Phe Asp Arg Ile Tyr Glu Ile
                165                 170                 175

Phe Trp Leu Asn Val Phe Gly Pro Lys Leu Val Glu Ala Val Gly Arg
            180                 185                 190

Glu Arg Met Leu Ser Thr Pro Ala His Arg Val Glu Glu Leu Pro Asn
        195                 200                 205

Gly Ser Ile Leu Leu Val Thr Trp Pro Thr Ala Ala Asp Phe Ala Gly
    210                 215                 220

Ala Glu Ala Arg His Ala Gln Ala Arg Ala His Val His Leu Arg Pro
225                 230                 235                 240

Asp Leu Arg Phe Asp Thr Val Leu Arg Thr Leu His Glu Arg Ser Ala
                245                 250                 255

Ala Leu Ala Pro Val Glu Pro Cys Phe His Pro Asp Val Ala Pro Leu
            260                 265                 270

Leu Ser His Val Val Asp Ser Val Ala Ile Arg Met Trp Lys Thr Trp
        275                 280                 285

Ser Ala Leu Thr Ser Ile Thr Glu Leu Trp Leu Ser Thr Ser Trp Arg
    290                 295                 300
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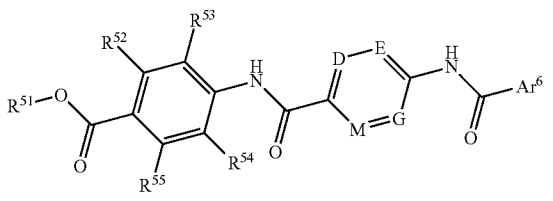
1. A compound of formula (V)



(V)

wherein

R^{51} is a hydrogen atom, or a C_{1-6} alkyl group;

R^{52} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{53} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{54} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{55} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

D is N or CR^{56};

E is N or CR^{57};

G is N or CR^{58};

M is N or CR^{59};

R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

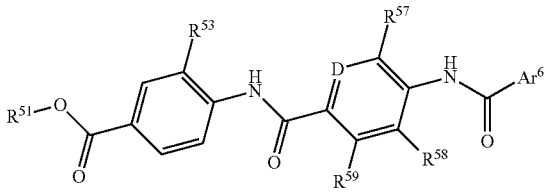
R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl; and

Ar^6 is an optionally substituted phenyl group or an optionally substituted heteroaryl group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

2. A compound according to claim **1** of formula (VI)

(VI)



wherein

R^{51} is a hydrogen atom, or a C_{1-6} alkyl group;

R^{53} is F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

D is N or CR^{56};

R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

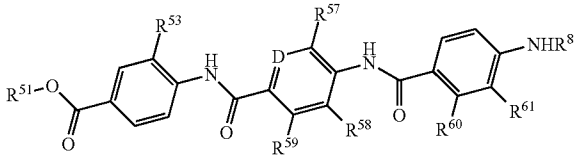
R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl; and

Ar^6 is an optionally substituted phenyl group or an optionally substituted heteroaryl group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

3. A compound according to claim **1** of formula (VII)

(VII)



wherein

R^{51} is a hydrogen atom, or a C_{1-6} alkyl group;

R^{53} is F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

D is N or CR^{56};

R^{56} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{57} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{58} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{59} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

R^{60} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl;

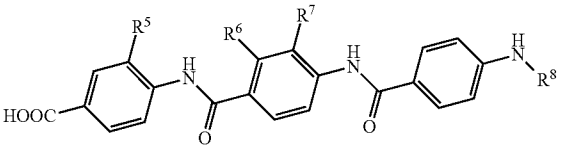
R^{61} is a hydrogen atom, F, Cl, a hydroxy group, a C_{1-6} alkyl group or a group of formula —O—C_{1-6} alkyl; and

R^8 is a hydrogen atom, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group;

or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

4. A compound according to claim **1** of formula (IV)

(IV)



wherein

R^5 is a group of formula —O—C_{1-6} alkyl;

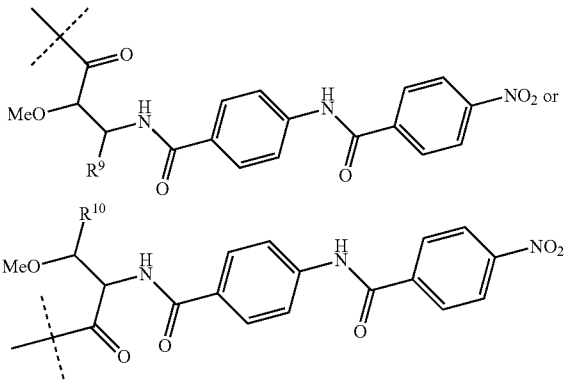
R^6 is a hydroxy group;

R^7 is a group of formula —O—C_{1-6} alkyl; and

R^8 is a hydrogen atom, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group;

or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

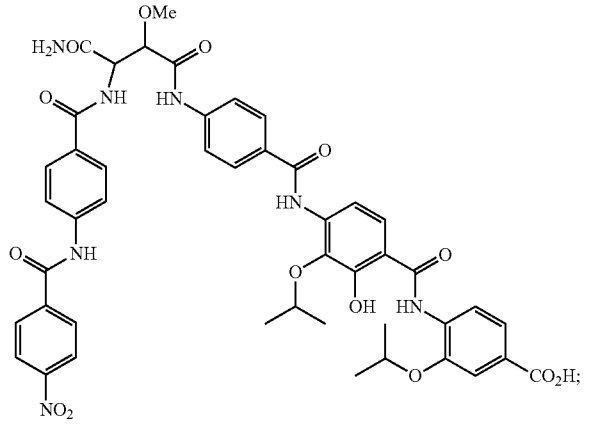
5. A compound according to claim **3**, wherein R^8 is a hydrogen atom or a group of the following formula:



wherein R^9 is COOH or $CONH_2$ and R^{10} is COOH or $CONH_2$.

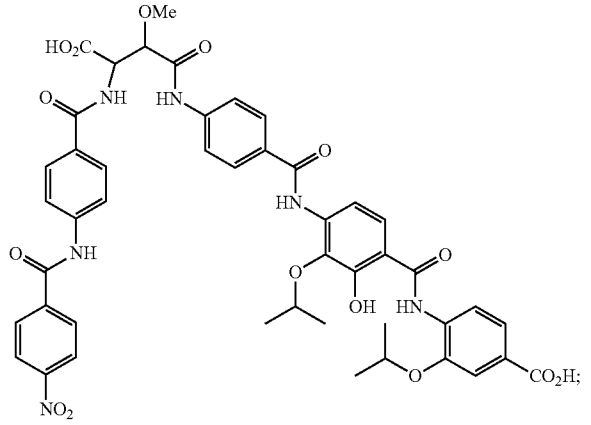
6. A compound selected from:

(1)



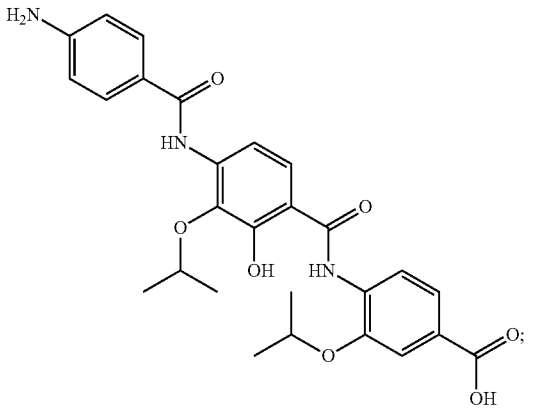
Cystobactamide A

(2)



Cystobactamide B

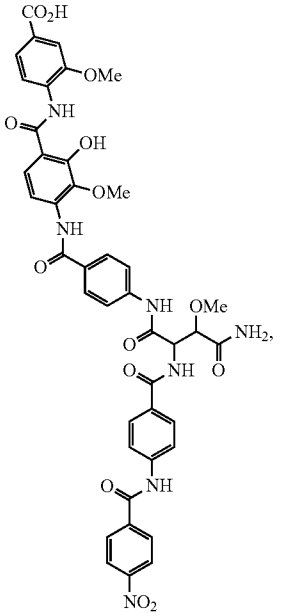
(3)



Cystobactamide C

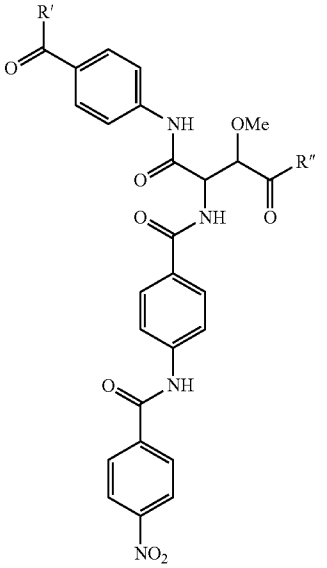
-continued

(4)



Cystobactamide D

(5)

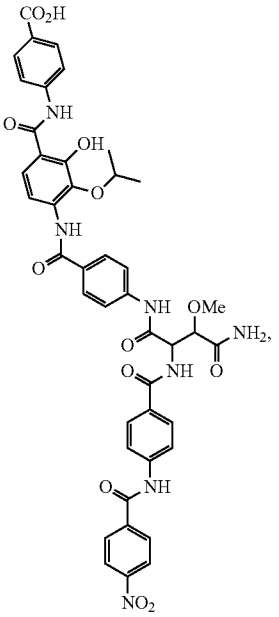


Cystobactamide E

(R' is NH_2 or OH and R'' is NH_2 or OH)

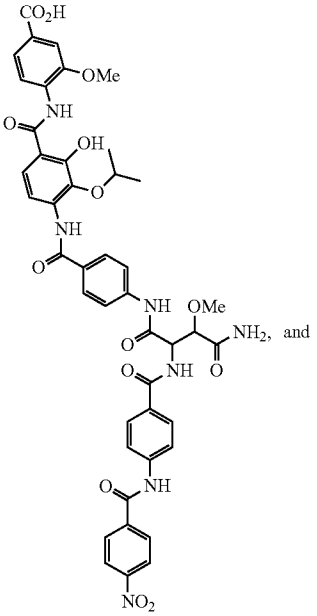
-continued

(6)



Cystobactamide F

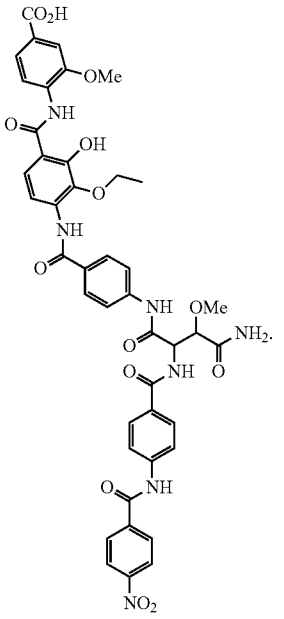
(7)



Cystobactamide G

-continued

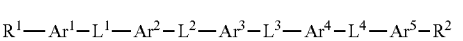
(8)



Cystobactamide H

7. A compound of formula (I)

(I)



wherein

Ar^1 is an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^2 is an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^3 is an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^4 is absent or an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^5 is absent or an optionally substituted phenylene group or an optionally substituted heteroarylene group having 5 or 6 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen;

L^1 is a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, —CNR^3—, —CO—, —SO—, —SO_2—, —SO_2NH—, —$NHSO_2$—, —SO_2NR^3—, —NR^3SO_2—, —$COCH_2$—, —CH_2CO—, —$COCR^3R^4$—, —CR^3R^4CO—, —NHCSNH—, —NR^3CSNR^4, —CH═CH—, —CR^3═CR^4—, or a heteroarylene group having 5 or 6

ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

L^2 is a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, $—CNR^3—$, —CO—, —SO—, $—SO_2—$, $—SO_2NH—$, $—NHSO_2—$, $—SO_2NR^3—$, $—NR^3SO_2—$, $—COCH_2—$, $—CH_2CO—$, $—COCR^3R^4—$, $—CR^3R^4CO—$, —NHCSNH—, $—NR^3CSNR^4$, —CH═CH—, $—CR^3═CR^4—$, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

L^3 is absent or a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, $—CNR^3—$, —CO—, —SO—, $—SO_2—$, $—SO_2NH—$, $—NHSO_2—$, $—SO_2NR^3—$, $—NR^3SO_2—$, $—COCH_2—$, $—CH_2CO—$, $—COCR^3R^4—$, $—CR^3R^4CO—$, —NHCSNH—, $—NR^3CSNR^4$, —CH═CH—, $—CR^3═CR^4—$, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

L^4 is absent or a bond, an oxygen atom, a sulphur atom or a group of formula NH, CONH, NHCO, COO, OCO, $CONR^3$, NR^3CO, OCONH, NHCOO, NHCONH, $OCONR^3$, NR^3COO, NR^3CONR^4, NR^3, $—CNR^3—$, —CO—, —SO—, $—SO_2—$, $—SO_2NH—$, $—NHSO_2—$, $—SO_2NR^3—$, $—NR^3SO_2—$, $—COCH_2—$, $—CH_2CO—$, $—COCR^3R^4—$, $—CR^3R^4CO—$, —NHCSNH—, $—NR^3CSNR^4$, —CH═CH—, $—CR^3═CR^4—$, or a heteroarylene group having 5 or 6 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, or a heteroalkylene group;

R^1 is a hydrogen atom, a halogen atom, a hydroxy group, an amino group, a thiol group, a nitro group, a group of formula —COOH, $—SO_2NH_2$, $—CONH_2$, $—NO_2$ or —CN, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group;

R^2 is a hydrogen atom, a halogen atom, a hydroxy group, an amino group, a thiol group, a nitro group, a group of formula —COOH, $—SO_2NH_2$, $—CONH_2$, $—NO_2$ or —CN, an alkyl, an alkenyl, an alkynyl, a heteroalkyl, a cycloalkyl, a heterocycloalkyl, an alkylcycloalkyl, a heteroalkylcycloalkyl, an aryl, a heteroaryl, an aralkyl or a heteroaralkyl group;

the groups R^3 are independently from each other a hydrogen atom or a C_{1-6} alkyl group; and

the groups R^4 are independently from each other a hydrogen atom or a C_{1-6} alkyl group;

or a pharmaceutically acceptable salt, solvate or hydrate or a pharmaceutically acceptable formulation thereof.

8. A compound according to claim **7** of formula (II)

$$R^1—Ar^1—L^1—Ar^2—L^2—Ar^3—R^2 \quad (II)$$

wherein

Ar^1, Ar^2, Ar^3, L^1, L^2, R^1 and R^2 are as defined in claim **7**.

9. A compound according to claim **7**, wherein

Ar^1 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^2 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^3 is an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen;

Ar^4 is absent or an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen; and

Ar^5 is absent or an optionally substituted 1,4-phenylene group or an optionally substituted 1,3-heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen.

10. A compound according to claim **7**, wherein

L^1 is a group of formula —CONH—, —NHCO—, $—SO_2NH—$, $—NHSO_2—$, —CH═CH—, $—CR^3═CR^4—$ or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group;

L^2 is a group of formula —CONH—, —NHCO—, $—SO_2NH—$, $—NHSO_2—$, —CH═CH—, $—CR^3═CR^4—$ or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group;

L^3 is absent or a group of formula —CONH—, —NHCO—, $—SO_2NH—$, $—NHSO_2—$, —CH═CH—, $—CR^3═CR^4—$ or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group; and

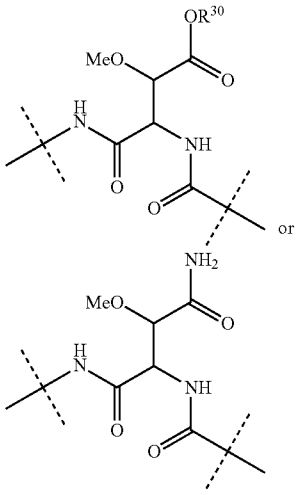
L^4 is absent or a group of formula —CONH—, —NHCO—, $—SO_2NH—$, $—NHSO_2—$, —CH═CH—, $—CR^3═CR^4—$ or an optionally substituted heteroarylene group having 5 ring atoms including 1, 2, or 3 heteroatoms selected from oxygen, sulphur and nitrogen, wherein R^3 and R^4 are independently from each other a C_{1-6} alkyl group.

11. A compound according to claim **7**, wherein R^1 is a hydrogen atom, a halogen atom or a group of formula —OH, $—NH_2$, —COOH, $—SO_2NH_2$, $—CONH_2$, $—NO_2$, —CN, -alkyl (e.g. $—CF_3$), —O-alkyl, —O—CO-alkyl, —NH-alkyl, —NH—CO-alkyl, or an optionally substituted heteroaryl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen, or

an optionally substituted heterocycloalkyl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen.

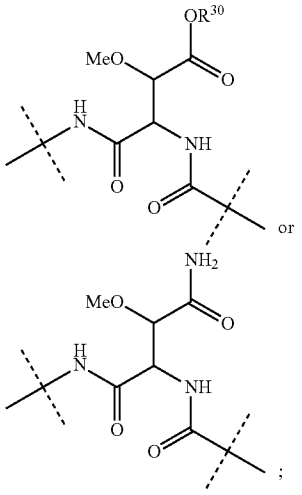
12. A compound according to claim **7**, wherein R^2 is a hydrogen atom, a halogen atom or a group of formula —OH, —NH_2, —COOH, —SO_2NH_2, —$CONH_2$, —NO_2, —CN, -alkyl (e.g. —CF_3), —O-alkyl, —O—CO-alkyl, —NH-alkyl, —NH—CO-alkyl, or an optionally substituted heteroaryl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen, or an optionally substituted heterocycloalkyl group having 5 ring atoms including 1, 2, 3 or 4 heteroatoms selected from oxygen, sulphur and nitrogen.

13. A compound according to claim **7**, wherein L^1 is NHCO (wherein the nitrogen atom is bound to Ar^1) or a group of the following formula:



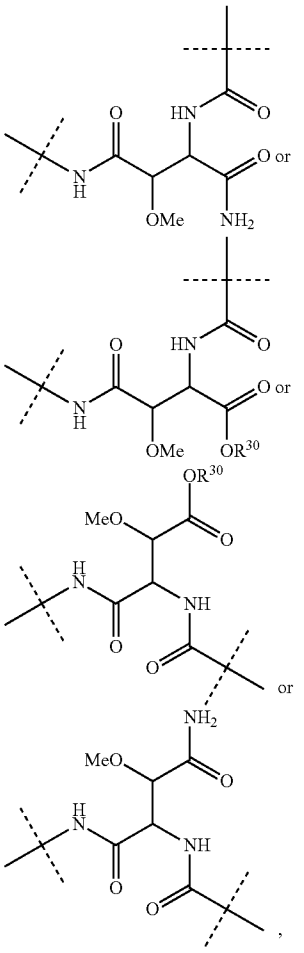
(wherein the NH group is bound to Ar^1), wherein R^{30} is a hydrogen atom or a C_{1-3} alkyl group; and/or

L^2 is NHCO (wherein the nitrogen atom is bound to Ar^2) or a group of the following formula:



(wherein the NH group is bound to Ar^2), wherein R^{30} is a hydrogen atom or a C_{1-3} alkyl group; and/or

wherein L^3 is absent or a group of the following formula:



(wherein the NH group is bound to Ar^3), wherein R^{30} is a hydrogen atom or a C_{1-3} alkyl group; and/or

wherein L^4 is absent or NHCO (wherein the nitrogen atom is bound to Ar^4).

14. Pharmaceutical composition comprising a compound according to claim **7**, and optionally one or more carrier substances and/or one or more adjuvants.

15. Compound or pharmaceutical composition according to claim **7**, for use in the treatment or prophylaxis of bacterial infections.

16. A recombinant biosynthesis cluster capable of synthesizing a cystobactamide selected from the group consisting of cystobactamide A, B, C, D, E, F, G and H, wherein the cluster comprises all of the polypeptides, or a functional variant thereof, according to SEQ ID NOs. 40 to 73.

17. An isolated, synthetic or recombinant nucleic acid comprising:

(i) a sequence encoding a cystobactamide biosynthesis cluster, wherein the sequence has a sequence identity to the full-length sequence of SEQ ID NO. 1 from at least 85%, 90%, 95%, 96%, 97%, 98%, 98.5%, 99%, or 99.5% to 100%;

(ii) a sequence encoding a NRPS, wherein the sequence has a sequence identity to the full-length sequence of any of SEQ ID NOs. 8, 9, 12 or 13 from at least 85%, 90%, 95%, 96%, 97%, 98%, 98.5%, 99%, or 99.5% to 100%;

(iii) a sequence completely complementary to the full length sequence of any nucleic acid sequence of (i) or (ii); or

(iv) a sequence encoding a polypeptide according to any of SEQ ID NOs. 46, 47, 50 or 51.

18. A vector comprising at least one nucleic acid according to claim **17**.

19. A recombinant host cell comprising at least one nucleic acid according to claim **17**.

20. A method for the preparation of a compound according to claim **6**, the method comprising the steps of:

(a) culturing *Cystobacter velatus* strain MCy8071 (DSM27004) or a recombinant host cell of claim **19**; and

(b) separating and retaining the compound from the culture broth.

21. A method for treating a subject suffering from or susceptible to a bacterial infection, comprising administering to the subject an effective amount of a compound of claim **7**.

22. The method of claim **21** wherein the subject is identified as suffering from a bacterial infection and the compound is administered to the identified subject.

23. The method of claim **21** wherein the subject is a human.

24. A method for treating a subject suffering from or susceptible to a bacterial infection, comprising administering to the subject an effective amount of a compound of claim **1**.

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