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- (54) Benævnelse: **GULD(III)-KOMPLEKS, ET KONJUGAT AF GULD(III)-KOMPLEKS, EN FARMAKOLOGISK SAMMENSÆTNING, DER OMFATTER GULD(III)-KOMPLEKSET, OG ANVENDELSER OG EN FREMGANGSMÅDE TIL FORBEREDELSE AF GULD(III)-KOMPLEKSET**
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RICHARD V. PARISH ET AL: "Chemical and Biological Studies of Dichloro(2-((dimethylamino)methyl)phenyl)gold(III)", INORGANIC CHEMISTRY, vol. 35, no. 6, 1 January 1996 (1996-01-01), pages 1659-1666, XP55514341, EASTON, US ISSN: 0020-1669, DOI: 10.1021/ic950343b

DescriptionTechnical Field

5 **[0001]** The present invention is directed, in general, to pharmaceutical compounds. In particular, the invention relates to a gold(III) complex, having formula (I), to be used as antibacterial and/or antibiofilm agents.

Background of the Invention

10 **[0002]** The rapid emergence of bacteria and other microorganisms is jeopardizing the efficacy of antibiotics, which have transformed medicine and saved millions of human and animal lives. Multiresistant bacteria are a global threat, estimated to cause 700,000 deaths worldwide each year. By the year 2050, 10 million people will die every year in the world from bacterial infections. They would exceed 1.8 million deaths from cancer. Recently, WHO has identified a group of multiresistant bacteria that are able to "escape" from the biocidal action of all known antibiotics and represent new
15 paradigms in pathogenesis, transmission and resistance bacteria of particular concern include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* (PAO) and *Enterobacteriaceae* species.

[0003] Gold(I) complexes have historically been studied as antimicrobial agents. A relevant example is the gold(I) complex auranofin, a drug initially approved as an antirheumatic agent, which also possesses potent antibacterial activity.

20 **[0004]** On the contrary, although gold(III) complexes have been intensively investigated as possible antitumor agents due to their similarities with platinum(II) complexes, until recently there were few references on their antibacterial activity. In recent years, the serious threat of resistant "superbugs" led to the evaluation of these antitumor drugs as well as antimicrobials, demonstrating antimicrobial activity against a wide range of pathogenic bacteria (Glisic, BD, et al., Dalton Trans. 2014, 43, 5950). The stabilization of the +3 oxidation state is of prime importance to observe any type of biological
25 activity. Otherwise, the metal center could be reduced, causing the formation of Au(0) and inactivation of the complex. In this regard, the advantage of organometallic cyclometalated gold compounds is their greater stability.

[0005] Taking into account the promising biological profile of cycloaurated complexes, the inventors of present invention have recently initiated an investigation into the rational design of a novel class of Au(III) complexes in which the metal center was integrated into a C,Y-metallacycle (Y = S, O). Using this concept, the inventors previously reported the
30 synthesis of (O[∧]C)- and (S[∧]C)-cycloaurated complexes based on an ortho-substituted phosphinic (Oña-Burgos, P, Fernández, I, Rocés, L, Torre-Fernández, L, García-Granda, S, López-Ortiz, F, Organometallics 2009, 28, 1739-1747) or thiophosphinic amide frameworks (Sánchez, EB, Iglesias, MJ, el Hajjouji, H, Rocés, L, García-Granda, S, Villuendas, P, Urriolabeitia, EP, López-Ortiz, F, Organometallics 2017, 36, 1962-1973), respectively, through tin(IV)-gold(III) transmetalation of the corresponding ortho chlorodimethylstannyl derivatives.

35 **[0006]** Besides that, therapeutic applications of gold(III) complexes focus primarily on anticancer properties (Ronconi, L et al., Adv. Anticancer Agents Med. Chem. 2013, 2, 130-172). With the rise of the threat of antibiotic resistance, increasing attention is being given to the antimicrobial properties of this compound class.

[0007] Gold(III) complexes tested for antimicrobial activity are either simple salts of Au(III) (e.g., tetrachlorides, carboxylates, etc. Borhade, S, Int. Res. J. Pharm. 2012, 3, 189-193. Al-Khodir, F.A.I, Refat, M.S. J. Pharm. Innov. 2015,
40 10, 335-347. Glisic, BD., et al MedChemComm 2016, 7, 1356-1366) or cyclometalates involving C[∧]N chelating ligands, usually aromatic nitrogen-containing heterocycles such as 2,2'-bipyridine, 2,2':6',2"-terpyridine, quinoline, 1,10-phenanthroline, etc. (Glisic, BD., Djuran, MI, Dalton Trans. 2014, 43, 5950-5969. Pintus, A, et al. J. Inorg. Biochem. 2017, 170, 188-194. Mignani, SM, et al. Mol. Pharmaceutics 2017, 14, 4087-4097.

[0008] Very recently, the behavior of complexes of NHet-AuCl₃ (NHet = pyrazine, pyrimidine, piridazine, quinoxaline and phenazine) (Savic, ND, et al. RSC Advances 2016, 6, 13193-13206) and C[∧]N-stabilized gold(III) cyclometalates (Radulovic, NS, et al. Polyhedron 2018, 141, 164-180) as antibiofilm agents has been reported.

[0009] Concerning gold(III) complexes containing a dithiocarbamate moiety, it has been described that the corresponding cycloaurates derived from phosphazenes showed in *vitro* anticancer activity against HeLa human cervical carcinoma and Jurkat-T acute lymphoblastic leukemia cells (Shaik, N et al. Inorg. Chem. 2009, 48, 1577-1587. L. Vela et al. J. Inorg. Biochem. 2011, 105, 1306).

[0010] Apart from that, there is one report in which C[∧]N-stabilized gold(III) cyclometalates (three examples involving the chelating ligand 2-((dimethylamino)methyl)phenyl) bearing a dithiocarbamate ligand) were investigated as antibacterial and antifungal agents. The complexes were less active than the control antibiotics, ciprofloxacin and amphotericin (Parish, RV, Inorg. Chem. 1996, 35, 1659). There are no precedents on the antimicrobial and antibiofilm therapeutic
55 properties of gold(III) complexes of formula (I) in which the Au(III) is part of a C-C-P-S-Au metallacycle.

Brief Description of the Invention

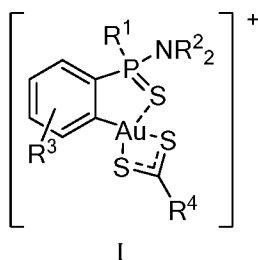
[0011] An object of the present disclosure is to provide stable cyclometalated gold(III) complexes having efficacy against a variety of microorganisms and low toxicity.

[0012] A group of (S⁺C)-cyclometalated gold(III) complexes containing a 1,1-dithio ligand, as represented in formula (I), which exhibit antibacterial activity against multiresistant microorganisms in planktonic or biofilm state, especially *S. aureus*, *S. maltophilia*, PAO, and *H. influenzae* (i.e. avoid the formation of biofilms of bacteria or eliminate those already formed). Thus, a new therapeutic tool to treat the infections caused by these bacteria is provided.

[0013] In addition, the compounds of formula (I) are not only highly active, as determined by *in vitro* tests, but are also highly stable under physiological conditions so they are expected to maintain their antibacterial activity *in vivo* in the same way.

[0014] Additionally, *in vitro* and *in vivo* assays show low toxicity of the compounds of formula (I).

[0015] According to a first aspect, the present disclosure relates to a gold(III) complex having formula (I):



wherein:

R¹ is independently selected from aryl and amine;

R² is independently selected from alkyl and cycloalkyl;

R³ is independently selected from hydrogen, halogen, nitro, cyano, alkyl, alkyloxy, alkylamino, aminodialkyl, hydroxyalkyl, trialkylsilyl, aryldialkylsilyl, alkylthio, cycloalkyl, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative; and

R⁴ is independently selected from alkyl, cycloalkyl, alkylalkoxy, alkylamino, dialkylamino, alkylthio, trialkylphosphino, dialkylarylphosphino, alkylarylphosphino, triarylphosphino, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative.

[0016] In an embodiment, binuclear complexes analogous to (I) are included. In this regard, a complex with two type (I) structures connected by a piperazine ring is used. Likewise, homo and heterobinuclear complexes can be used. They include complexes prepared using a R⁴ substitute that has coordination positions to another metal.

[0017] In an embodiment, the radicals that can be used are:

- R¹ = phenyl, and N(R²)₂, being R² = dialkyl (i.e. N(R²)₂ = N(*i*Pr)₂, N(Et)₂, piperazine);
- R³ = hydrogen;
- R⁴ = aliphatic amine such as NMe₂, NEt₂, N(CH₂Ph)₂, pyrrolidyl, piperidinyl, and azepanyl links, or heterocyclical including piperazinyl or morpholinyl; and
- R⁴ as ligand for dinuclear complexes, for example piperazine, i.e. a homonuclear complex. The amine can easily be changed to include a second electron donor atom (the simplest way is to use amines with heterocyclic systems such as pyridine or azoles. That leaves a second position to coordinate other metals, for example, AuCl-L (L = Ph₃P, tetrahydrothiophene), AuCl₃ and copper salts.

[0018] Another aspect of the present invention relates to a conjugate comprising the cited gold(III) complex of formula (I) and at least one carrier, preferably a pharmaceutical carrier.

[0019] Another aspect of the present invention relates to a pharmaceutical composition comprising the cited gold(III) complex of formula (I) or the above-mentioned conjugate and at least one pharmaceutically acceptable excipient.

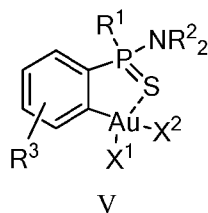
[0020] In an embodiment, the gold(III) complex, the conjugate or the pharmaceutical composition is used in the manufacture of a medicament, for example for the treatment of a microbial infection.

[0021] In another embodiment, the gold(III) complex, the conjugate or the pharmaceutical composition is used as a medicament in the treatment and/or prevention of bacterial infections caused by multiresistant bacteria or other microorganisms.

[0022] In another embodiment, the gold(III) complex, the conjugate or the pharmaceutical composition is used to inhibit biofilm formation or development, to eliminate mature biofilms and/or to reduce the biofilm biomass.

[0023] Another aspect of the present invention relates to a process for preparing the gold(III) complex of formula (I), comprising reacting a compound of formula (V)

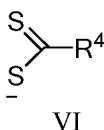
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with a compound of formula (VI)

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and subsequent formation of a pharmaceutically stable salt or solvate of the resulting complex by treatment with an organic or inorganic acid or their corresponding salts, wherein:

- 25 X^1 is independently selected from halogen, hydroxide or acetoxy;
 X^2 is independently selected from halogen, hydroxide or acetoxy;
 R^1 is independently selected from aryl and amine;
 R^2 is independently selected from alkyl and cycloalkyl;
 R^3 is independently selected from hydrogen, halogen, nitro, cyano, alkyl, alkyloxy, alkylamino, aminodialkyl, hydroxyalkyl, trialkylsilyl, aryldialkylsilyl, alkylthio, cycloalkyl, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative; and
 R^4 is independently selected from alkyl, cycloalkyl, alkylalkoxy, alkylamino, dialkylamino, alkylthio, trialkylphosphino, dialkylarylphosphino, alkylarylphosphino, triarylphosphino, aryl, heterocycle, polycycle, amino, acid, peptide and carbohydrate derivative.

35

Brief Description of the Drawings

[0024] The previous and other advantages and features will be more fully understood from the following detailed description of embodiments, with reference to the attached figures, which must be considered in an illustrative and non-limiting manner, in which:

40

Fig. 1 shows the structure of complex 2b

Fig. 2 shows the structure of complex 2f

Fig. 3 shows the structure of complex 2g

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Fig. 4 shows the structure of complex 2n

Fig. 5 is a view of the molecular structure of complex 2g, with partial atom labelling scheme and displacement ellipsoids drawn at 50% probability level.

Fig. 6 is a graph showing the toxicity of 2g.

Fig. 7 is a $^1\text{H-NMR}$ spectrum of complex 2b

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Fig. 8 is a $^{13}\text{C-NMR}$ spectrum of complex 2b

Fig. 9 is a $^{31}\text{P-NMR}$ spectrum of complex 2b

Fig. 10 is a $^1\text{H-NMR}$ spectrum of complex 2g

Fig. 11 is a $^{13}\text{C-NMR}$ spectrum of complex 2g

Fig. 12 is a $^{31}\text{P-NMR}$ spectrum of complex 2g

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Fig. 13 is a $^{31}\text{P-NMR}$ spectrum of complex 2f in 0.25 mL $\text{CD}_3\text{CN}/0.25$ mL of phosphate buffer, at 37 $^\circ\text{C}$, taken immediately after dissolution.

Fig. 14 is a $^{31}\text{P-NMR}$ spectrum of complex 2f in 0.25 mL $\text{CD}_3\text{CN}/0.25$ mL of phosphate buffer, at 37 $^\circ\text{C}$, taken 3 days after dissolution.

Fig. 15 is a ^{31}P -NMR spectrum of complex 2f in 0.25 mL CD_3CN and ISO culture broth in 0.25 mL of D_2O .

Fig. 16 is a ^{31}P -NMR spectrum of complex 2f in 0.25 mL CD_3CN and 1 equiv. of glutathione in 0.25 mL of H_2O .

Fig. 17 is a ^{31}P -NMR spectrum of complex 2f in 0.25 mL CD_3CN and 1 equiv. of ascorbic acid in 0.25 mL of H_2O .

5 Detailed Description of Preferred Embodiments

[0025] Present invention relates in a first embodiment to a gold(III) complex having formula (I):



wherein:

- 20
- R^1 is independently selected from aryl and amine
 R^2 is independently selected from alkyl and cycloalkyl
 R^3 is independently selected from hydrogen, halogen, nitro, cyano, alkyl, alkyloxy, alkylamino, aminodialkyl, hydroxyalkyl, trialkylsilyl, aryldialkylsilyl, alkylthio, cycloalkyl, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative
 R^4 is independently selected from alkyl, cycloalkyl, alkylalkoxy, alkylamino, dialkylamino, alkylthio, trialkylphosphino, dialkylarylphosphino, alkylarylphosphino, triarylphosphino, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative.
- 25

30 **[0026]** The compounds of formula (I) contain a positive charge and can form salts with organic or inorganic acids. Therefore, pharmaceutically acceptable salts of the compounds of formula (I) are also included within the scope of the invention. Any reference to a compound of formula (I) throughout the description includes a reference to any pharmaceutically acceptable salt of such compound of formula (I). The term "pharmaceutically acceptable salts", as used herein, encompasses any salt without any limitation on the salt that can be used, provided that these are acceptable for administration to a patient. For example, pharmaceutically acceptable salts include chloride, bromide, malonate, pyruvate, etc. Hexafluorophosphate is preferred.

35

[0027] In another embodiment, the invention relates to compounds of formula (I) having a minimum inhibitory concentration (MIC) of 0.125-0.5 mg/L for *S. aureus*, of 2-4 mg/L for *S. maltophilia* and of 1-2 mg/L for *H. influenzae*, being lower than the MICs of other antibiotics used in the treatment infections caused by these microorganisms, as described in example 2 for *S. aureus*. As shown in the example, the compounds of the present invention showed high antibacterial activity against a series of strains resistant to methicillin, clindamycin, erythromycin, ciprofloxacin, with values of minimum inhibitory concentration (MIC) equal to or less than 0.5 mg/L for all the compounds tested.

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[0028] Therefore, present invention also provides a compound of formula (I) or any pharmaceutically acceptable salt for its use in the manufacture of a medicament for the treatment and/or prevention of a microbial infection.

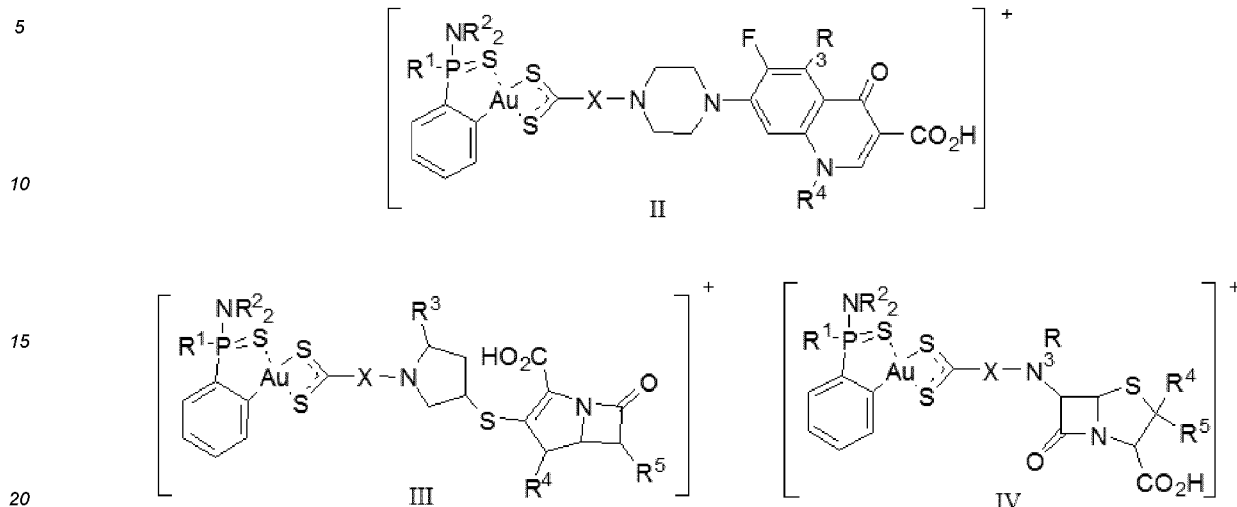
45 **[0029]** In another embodiment, the present invention relates to a compound of formula (I) for use as an antimicrobial agent for the treatment of a human or animal patient afflicted with an infection by multiresistant microorganisms, including the administration to said patient of an effective amount of a pharmaceutical composition containing the compound of formula (I). As shown in example 3, compounds of formula (I) have resulted in low-null toxicity in mice at doses greater than 5 mg/kg in weight, much higher than the concentration at which it is active.

50 **[0030]** In another embodiment, due to the high activity of the compounds of formula (I) against multiresistant microorganisms, these compounds can be used in combination with other antimicrobials, typically broad spectrum antibiotics, to thereby enhance the antimicrobial efficacy of the therapy. Compounds of formula (I) can be combined with any type of antimicrobial agent used in therapy, as (but not limited to) vancomycin, daptomycin, fosfomycin, ciprofloxacin or imipenem.

55 **[0031]** The combination of compounds of formula (I) with an additional antimicrobial agent can be achieved by administering both substances as a fixed dose combination in pharmaceutical dosage form or, alternatively, both drugs can be administered independently, according to a therapeutic combination regimen.

[0032] Alternatively, the compound of formula (I) can be combined with another antibacterial agent by covalently

bonding both compounds to form a single molecule. For example, the compound of formula (I) can be linked to an antibacterial compound of fluoroquinolone, carbapenemic or penicillin derivative, according to formulas (II-IV).



[0033] In another embodiment, the biosynthetic pathways involved in the antibacterial activity of compound of formula (I) are studied. Their possible role in the interaction with intracellular proteins and enzymes, in the catalysation of various intracellular processes, in the ability of mutating the bacterial DNA and/or in the overexpression or repression of genes and the consequent proteins is studied using proteomics, genomics and microscopic approaches.

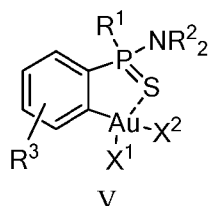
[0034] In another embodiment, present invention relates to a pharmaceutical composition comprising a compound of formula (I) and at least one acceptable pharmaceutical excipient or carrier.

[0035] Another embodiment of the present invention relates to the use of the compounds of the present invention to inhibit the formation or development of biofilm, eliminating existent biofilms, and reducing the biofilm biomass.

[0036] A method for inhibiting biofilm formation is also proposed, including exposing formed biofilms to an effective amount of the compound of the invention for eradication. Thus, as shown in example 4, compounds of formula (I) have minimal Biofilm Inhibition Concentrations (MBIC) lower than antibiotics used in the treatment of these infections as in the case of *S. aureus*.

[0037] In some embodiments, the compound of the invention is impregnated or deposited on the surface susceptible to biofilm formation.

[0038] The surface can be the surface of a medical instrument such as: surgical equipment, implants or prostheses, catheters (urinary or venous), stents, pacemakers, dialysis equipment, heart valves and medical fixation instruments (plates, screws, nails ...). Another embodiment of the present invention relates to a process for the preparation of a compound of formula (I) (as defined above) which comprises reacting a compound of formula (V)



wherein:

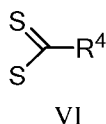
X¹ is independently selected from halogen, hydroxide or acetoxy

X² is independently selected from halogen, hydroxide or acetoxy

R¹ is independently selected from aryl and amine

R² is independently selected from alkyl and cycloalkyl

R³ is independently selected from hydrogen, halogen, nitro, cyano, alkyl, alkoxyalkyl, aminoalkyl, aminodialkyl, hydroxyalkyl, trialkylsilyl, arylalkylsilyl, alkylthio, cycloalkyl, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative with a compound of formula (VI)

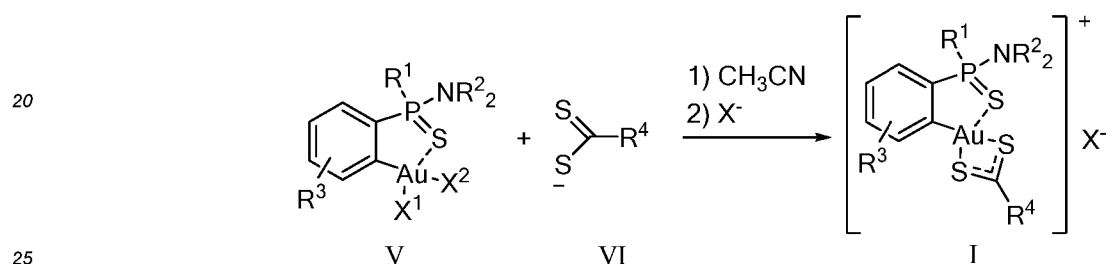


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wherein:

10 R^4 is independently selected from alkyl, cycloalkyl, alkylalkoxy, alkylamino, dialkylamino, alkylthio, trialkylphosphino, dialkylarylphosphino, alkylarylphosphino, triarylphosphino, aryl, heterocycle, polycycle, amino acid, peptide and carbohydrate derivative, and subsequent formation of a pharmaceutically stable salt or solvate of the resulting complex by treatment with an organic or inorganic acid or their corresponding salts.

15 **[0039]** The procedure can be represented according to Scheme I:

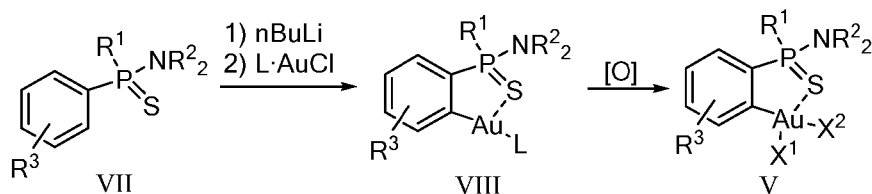


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[0040] The present invention also relates to a method for the preparation of compound V, consisting of the ortho-metallation of a thiophosphinic or thiophosphonic amide framework, followed by transmetalation with a gold(I) salt and oxidation to gold(III), as represented in Scheme II:

30



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wherein:

40 L is independently selected from a tertiary phosphine (Flower, KR, et al. Dalton Transactions 2010, 39, 3509-3520), a tertiary arsine (Pena-López, M, et al Org. Biomol. Chem. 2012, 10, 1686-1694) or a thioether (Espinet, P, Organometallics, 2000, 19, 290-295).

[0041] It should be mentioned that the derivative of compound V were $R^1 = \text{NEt}_2$, $\text{N}(\text{R}^2)_2 = \text{NEt}_2$, $R^3 = \text{H}$, $\text{X}^1 = \text{X}^2 = \text{Cl}$ has been already synthesized by Kilpin, K.J. et al. (Dalton Trans. 2010, 39, 1855-1864) via Hg(II)/Au(III) exchange, i.e., a procedure different from the method described in the present patent application (Sn(IV)/Au(III) exchange).

[0042] The oxidant agent is selected from X_2 (Viente, J, Arcas, A, Marc, M, J. Organomet. Chem 1986, 309, 3689-378), PhIX_2 (Hofer, M., Gomez-Bengoia, E, Nevado, C, Organometallics 2014, 33, 1328-1332) or CF_3I (Winston, MS, Wolf, WJ, Toste, FD, J. Am. Chem. Soc. 2014, 136, 7777-7782).

[0043] Alternatively, complex (V) can be prepared by boron/Au(III) metathetical reactions using the corresponding ortho borinated derivative of phosphinothioic amide VII (Price, GA, et al. Dalton Trans., 2011, 40, 11696-11697).

[0044] The compounds of the present invention, as well as the intermediates, can be prepared by the methods described herein or small variations thereof, as well as by alternative methods.

[0045] Further aspects of the invention relate to the stability of the compounds of formula (I) in physiological conditions and in the presence of classical reducing agents and human serum albumine.

55

EXAMPLES

[0046] The following examples have been included to further describe protocols for the synthesis and evaluation of

the gold(III) complexes. It should be noted that these examples have been included for illustrative purposes, and are not intended to limit the scope of the invention.

Synthesis of gold(III) complexes

[0047] All reactions were carried out under inert atmosphere, in previously dried Schlenks. CH₃CN was distilled in the presence of P₂O₅ and degassed before use. Commercial reagents were used as received.

[0048] Synthesis of complexes 2: To a solution of Au(III) complex 1 (0.20 mmol) in CH₃CN (6 mL), the corresponding dithiocarbamate salt was added (0.20 mmol). The reaction mixture was stirred at rt for 12 h. After addition of aqueous saturated potassium hexafluorophosphate, the resulting solid was filtered and the residue was washed with water and diethyl ether to afford complexes 2 as bright yellow solids. The most relevant analytical data of selected gold complexes (III) are presented in Table 1.

NMR experiments

[0049] NMR spectra were obtained on a Bruker Avance III HD 300 (¹H 300.13 MHz; ¹³C 75.47 MHz; ³¹P 121.49 MHz) and Bruker Avance III HD 500 (¹H 500.13 MHz; ¹³C 125.76 MHz; ³¹P 202.46 MHz). Chemical shifts are given in ppm using tetramethylsilane (TMS) for ¹H and ¹³C as internal standards and 85% H₃PO₄ for ³¹P as external standard. ¹H, ¹H{³¹P} and ³¹P NMR spectra were acquired from all reaction crudes in CDCl₃ or CD₃CN as solvent. The following abbreviations are used to indicate the multiplicity of signal: s - singlet, d - doublet, t - triplet, q - quartet and sep - septet.

[0050] All the NMR spectra supported the structures of the synthesized compounds.

Mass spectroscopy

[0051] High Resolution Mass Spectra (HRMS) were recorded on an Agilent Technologies LC/MSD-TOF and HP 1100 MSD spectrometer using electrospray ionization.

[0052] The auracyclic complexes 2 have also been characterized by electrospray ionization mass spectrometry (ESI-MS), showing a strong peak due to the gold cation. Calculated isotopic clusters were in excellent agreement with the experimental ones.

Table 1.-

Structure	Name/Analytical data
Fig. 1	[Gold(III) 2-((diisopropylamino)(phenyl)phosphorothioyl)phenyl] (diethyldithiocarbamate) hexafluorophosphate
	¹ H NMR (300 MHz, CDCl ₃) δ 1.20 (d, ³ J _{PH} 6.8 Hz, 6H), 1.30 (d, ³ J _{PH} 6.8 Hz, 6H), 1.37 (q, ³ J _{HH} 7.0 Hz, 6H), 1.32 (d, ³ J _{PH} 6.8 Hz, 6H), 3.66-3.85 (m, 6H), 7.36 (ddd, 1H, ³ J _{HH} 7.8 Hz, ⁴ J _{PH} 3.6 Hz, ⁴ J _{HH} 1.2 Hz), 7.47 (tt, 1H, ³ J _{HH} 7.4 Hz, ⁵ J _{PH} 1.7 Hz, ⁴ J _{HH} 1.7 Hz), 7.54-7.70 (m, 4H), 7.77 (ddd, 1H, ³ J _{PH} 10.2 Hz, ³ J _{HH} 7.6 Hz, ⁴ J _{HH} 1.6 Hz), 7.98-8.32 (m, 2H) ppm. ¹³ C NMR (75 MHz, CDCl ₃) δ 12.3, 12.4, 23.0 (d, ³ J _{PC} 3.0 Hz), 23.3 (d, ³ J _{PC} 3.3 Hz), 50.7 (d, ² J _{PC} 3.2 Hz), 127.4 (d, ¹ J _{PC} 101.8 Hz), 128.5 (d, ³ J _{PC} 11.9 Hz), 129.6 (d, ³ J _{PC} 13.7 Hz), 132.4 (d, ³ J _{PC} 17.0 Hz), 131.7 (d, ² J _{PC} 13.2 Hz), 133.4 (d, ² J _{PC} 11.8 Hz), 134.7 (d, ⁴ J _{PC} 3.1 Hz), 135.3 (d, ⁴ J _{PC} 3.5 Hz), 138.6 (d, ¹ J _{PC} 124.1 Hz), 143.7 (d, ² J _{PC} 28.0 Hz), 194.5 ppm. ³¹ P-NMR (121 MHz, CDCl ₃) δ - 143.6 (h, ¹ J _{PF} 712.3 Hz), 76.4 ppm.
	HRMS (ESI ⁺) [M] ⁺ calcd. for C ₂₁ H ₂₉ AuN ₂ PS ₃ , 661.1023; found, 661.1019.
Fig. 2	[Gold(III) 2-((diisopropylamino)(phenyl)phosphorothioyl)phenyl] (pirrolidin-1-dithiocarbamate) hexafluorophosphate ¹ H NMR (300 MHz, CDCl ₃) δ 1.23 (d, ³ J _{PH} 6.8 Hz, 6H), 1.32 (d, ³ J _{PH} 6.8 Hz, 6H), 2.16-2.23 (m, 4H), 3.65-3.90 (m, 4H), 3.65-3.90 (m, 6H), 7.33 (ddd, ³ J _{HH} 7.8 Hz, ³ J _{PH} 3.6 Hz, ⁴ J _{HH} 1.7 Hz, 1 H), 7.46 (t, ³ J _{HH} 7.5 Hz, ³ J _{PH} 7.5 Hz, ⁴ J _{HH} 1.7 Hz, 1H), 7.54-7.79 (m, 5H), 8.02-8.17 (m, 2H) ppm. ¹³ C NMR (75 MHz, CDCl ₃) 23.1 (d, ³ J _{PC} 3.1 Hz), 23.4 (d, ³ J _{PC} 3.4 Hz), 24.0, 24.2, 50.7 (d, ² J _{PC} 3.3 Hz), 51.0, 51.6, 127.4 (d, ¹ J _{PC} 101.7 Hz), 128.4 (d, ³ J _{PC} 12.0 Hz), 129.6 (d, ³ J _{PC} 13.6 Hz), 132.6 (d, ³ J _{PC} 16.7 Hz), 133.1 (d, ² J _{PC} 12.2 Hz), 133.4 (d, ² J _{PC} 11.8 Hz), 134.7 (d, ⁴ J _{PC} 3.1 Hz), 135.3 (d, ⁴ J _{PC} 3.6 Hz), 138.4 (d, ¹ J _{PC} = 124.0 Hz), 144.1 (d, ² J _{PC} 27.7 Hz), 191.2 ppm. ³¹ P-NMR (121 MHz, CDCl ₃) δ -143.6 (h, ¹ J _{PF} 712.5 Hz), 76.2 ppm.
	HRMS (ESI ⁺) [M] ⁺ calcd. for C ₂₃ H ₃₁ AuN ₂ PS ₃ , 659.1047; found, 659.1043.

(continued)

Structure	Name/Analytical data
5	[Gold(III) 2-((diisopropylamino)(phenyl)phosphorothioyl)phenyl] (piperidin-1-dithiocarbamate)] hexafluorophosphate
10	Fig. 3 ¹ H NMR (600 MHz, DMSO-d ₆) δ 1.17 (d, ³ J _{PH} 6.8 Hz, 6H), 1.26 (d, ³ J _{PH} 6.8 Hz, 6H), 1.71-1.75 (m, 6H), 3.75 (dh, ² J _{HH} 18.2 Hz, ³ J _{HH} 6.8 Hz, 2H), 3.87-3.93 (m, 6H), 7.43-7.45 (m, 1H), 7.43-7.45 (m, 2H), 7.71-7.75 (m, 2H), 7.82 (td, 1H, ³ J _{HH} 7.4 Hz, ⁴ J _{HH} 1.7 Hz), 7.43-7.45 (m, 1H), 8.21-8.25 (m, 2H) ppm. ¹³ C NMR (150 MHz, DMSO-d ₆) 23.0 (d, ³ J _{PC} 3.0 Hz), 23.2 (d, ³ J _{PC} 3.2 Hz), 23.9, 25.6, 25.7, 50.7 (d, ² J _{PC} 3.0 Hz), 51.0, 51.1, 127.8 (d, ¹ J _{PC} 101.3 Hz), 128.9 (d, ³ J _{PC} 12.0 Hz), 130.1 (d, ³ J _{PC} 13.6 Hz), 132.8 (d, ³ J _{PC} 16.7 Hz), 133.8 (d, ² J _{PC} 12.0 Hz), 134.2 (d, ² J _{PC} 12.5 Hz), 135.3 (d, ⁴ J _{PC} 3.0 Hz), 136.0 (d, ⁴ J _{PC} 3.5 Hz), 139.0 (d, ¹ J _{PC} = 123.7 Hz), 144.1 (d, ² J _{PC} 28.0 Hz), 190.6 ppm. ³¹ P-NMR (121 MHz, CD ₃ CN) δ -143.9 (h, ¹ J _{PF} 706.2 Hz), 75.6 ppm.
15	HRMS (ESI ⁺) [M] ⁺ calcd. for C ₂₄ H ₃₃ AuN ₂ PS ₃ , 673.1204; found, 673.1244.
20	[Gold(III) 2-((diisopropylamino)(phenyl)phosphorothioyl)phenyl] (1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-4-dithiocarbamate-1-yl)-quinolin-3-carboxylic acid)] hexafluorophosphate
25	Fig. 4 ¹ H NMR (600 MHz, DMSO-d ₆) δ 1.17 (d, ³ J _{PH} 6.8 Hz, 6H), 1.26 (d, ³ J _{PH} 6.8 Hz, 6H), 1.71-1.75 (m, 6H), 3.75 (dh, ² J _{HH} 18.2 Hz, ³ J _{HH} 6.8 Hz, 2H), 3.87-3.93 (m, 6H), 7.43-7.45 (m, 1H), 7.43-7.45 (m, 2H), 7.71-7.75 (m, 2H), 7.82 (td, 1H, ³ J _{HH} 7.4 Hz, ⁴ J _{HH} 1.7 Hz), 7.43-7.45 (m, 1H), 8.21-8.25 (m, 2H) ppm. ¹³ C NMR (150 MHz, DMSO-d ₆) 8.1, 23.0 (d, ³ J _{PC} 3.3 Hz), 23.2 (d, ³ J _{PC} 3.2 Hz), 48.8, 49.2, 49.4, 50.7 (d, ² J _{PC} 2.9 Hz), 107.0, 111.8, 111.9, 127.5, 128.2, 129.0 (d, ³ J _{PC} 11.9 Hz), 130.1 (d, ³ J _{PC} 13.6 Hz), 132.8 (d, ³ J _{PC} 16.8 Hz), 133.8 (d, ² J _{PC} 12.0 Hz), 134.2 (d, ² J _{PC} 12.4 Hz), 135.3 (d, ⁴ J _{PC} 3.0 Hz), 136.2 (d, ⁴ J _{PC} 3.6 Hz), 138.8, 138.9 (d, ¹ J _{PC} = 123.7 Hz), 144.1 (d, ² J _{PC} 27.7 Hz), 147.8, 151.8, 153.4, 175.5, 166.8, 193.2 ppm. ³¹ P-NMR (121 MHz, CD ₃ CN) δ -114.6 (h, ¹ J _{PF} 713.2 Hz), 70.9, 76.2 ppm.
	HRMS (ESI ⁺) [M] ⁺ calcd. for C ₃₆ H ₄₀ AuFN ₄ O ₃ PS ₃ , 919.1650; found, 919.1667.

30 **[0053]** As representative examples, copies of NMR spectra for compounds 2b and 2g are shown in Figs. 7 to 12: ¹H- (Fig. 7), ¹³C- (Fig. 8), ³¹P (Fig. 9) NMR spectra of 2b; ¹H- (Fig. 10), ¹³C- (Fig. 11), ³¹P (Fig. 12) NMR spectra of 2g.

X-Ray diffraction

35 **[0054]** Single crystal X-ray diffraction data were collected on a Bruker D8 Venture diffractometer at 100 K, using CuK_α radiation (λ = 1.54178 Å). Data collection and cell refinement were performed with Bruker Instrument Service v4.2.2. Empirical multiscan absorption correction using equivalent reflections was performed with the SADABS program. The structure solution and full-matrix least-squares refinement based on F² was performed with CRYSTALS (Betteridge, PW, Carruthers, JR, Cooper, RI, Prout, K, Watkin, DJ, J. Appl. Cryst. 2003 36, 1487). All atoms except for hydrogen
 40 were refined anisotropically. Hydrogen atoms were treated by a mixture of independent and constrained refinement. A summary of crystal data and refinement details for compound 2g are given in Table 2. Fig. 5 was drawn using the program PLATON. Selected bond-distances and bond angles are given in Table 3.

Table 2.-

45	Bond precision:	C-C = 0.0077 Å		Wavelength=1.54180
	Cell:	a=13.2542(4)	b=25.8434(7)	c=8.9111(3)
50		alpha=90	beta=101.5753(13)	gamma=90
	Temperature:	100 K		
		Calculated	Reported	
55	Volume	2990.27(16)		2990.27(10)
	Space group	P 21/c		P 1 21/c 1

(continued)

Hall group	-P 2ybc	?
Moiety formula	C24 H33 Au N2 P S3, F6 P	C4 H5.50 Au0.17 F1 N0.33 P0.33 S0.50
Sum formula	C24 H33 Au F6 N2 P2 S3	C4 H5.50 Au0.17 F1 N0.33 P0.33 S0.50
Mr	818.61	136.44
Dx,g cm-3	1.818	1.818
Z	4	24
Mu (mm-1)	12.719	12.719
F000	1608.0	1608.0
F000'	1600.63	
h,k,lmax	15,30,10	15,30,10
Nref	4950	4937
Tmin,Tmax	0.433,0.579	0.560,0.760
Tmin'	0.201	
Correction method = # Reported T Limits: Tmin=0.560 Tmax=0.760 AbsCorr = GAUSSIAN		
Data completeness= 0.997	Theta(max)= 63.813	
R(reflections)= 0.0283(4349)	wR2(reflections)=0.0632(4914)	
S = 0.985	Npar= 443	

Table 3.-

<i>Bond lengths</i>			
Au1-S2	2.330(11)	Au1-S25	2.317(12)
Au1-S23	2.058(18)	Au1-C12	2.058(5)
<i>Bond angles</i>			
S2-Au1-S23	97.64(4)	S2-Au1-C12	90.68(13)
S23-Au1-S25	74.99(4)	C12-Au1-S23	171.69(13)
S4-Au1-S25	172.42(4)	S2-Au1-C24	134.35(16)

Stability studies of the gold (III) complexes 2

[0055] A solution of compound 2f in CD₃CN (0.25 mL) was mixed with 0.25 mL of saline phosphate buffer (pH 7.4) in D₂O and the mixture was monitored at 37 °C over three days through ¹H and ³¹P NMR spectroscopy. As illustrated in Figs. 13 and 14, the ³¹P NMR signal of the complex remained unaltered over the three-day period. Such observations show a substantial evidence for the stability of complexes 2 under physiological conditions.

[0056] Complexes 2 are also stable in the conditions used for the biological activity assays, as evidenced by the ³¹P NMR spectra of a solution of compound 2f in CD₃CN (0.25 mL) and 0.25 mL of ISOsensitest culture broth prepared in D₂O (Fig. 15).

[0057] To gain a more complete picture of the stability and the solution behavior of these gold(III) compounds 2, the spectral changes produced by addition of classical reducing agents, i.e. glutathione (GSH) and ascorbic acid (AsAc) were also examined. Thus, solutions of compound 2f in CD₃CN (0.25 mL) were mixed with solutions containing equimolar

amounts of either GSH or AsAc in 0.25 mL of H₂O. The ³¹P NMR spectra clearly indicated that the gold complex maintained its chemical integrity, as evidenced by the NMR spectra presented in Figs. 16 and 17.

Example 2. Antimicrobial activity.-

[0058]

Strain	Resistance profile	MIC formula (I) (mg/L)	MIC Ciprofloxacin (Cip) (mg/L)	MIC Levofloxacin (Lvx) (mg/L)
MRSA 1	Cip, Cli, Eri, Pen, Lvx	0.25	128	128
MRSA 2	Gen, Cip, Cli, Eri, Pen, Lvx	0.25	16	64
MRSA, methicillin resistant <i>S. aureus</i> ; Cip, ciprofloxacin; Cli, clindamycin; Eri, erythromycin; Pen, penicillin; Lvx, levofloxacin; Gen, gentamicin.				

[0059] This example evidenced the high antibacterial activity shown by the compound of formula (I) in comparison with Cip and Lvx, both antimicrobial agents used in the treatment of infection caused by MRSA. The compounds are active at concentrations until 9-fold lower (MIC 128 mg/L for Cip in contrast to 0.25 mg/L for formula (I) compound) than these antimicrobial agents.

Example 3. *In vivo* toxicity assay.-

[0060] Treatment: Single intravenous dose (100 µL) of 2-10 mg/kg of the compounds 2 (or formula (I)) and vehicle control groups DMSO.

[0061] Development: The animals were monitored for 2 weeks after the inoculation of the treatment. Signs of toxicity such as weight reduction, bristly coat, reduced mobility, ocular epiphora were verified. The animals were weighed each day until the end of the experiment. A decrease of 80% of the initial weight of the mouse was considered as an endpoint criterion.

[0062] Result: No significant differences in weight were observed in the dose of 2 mg/kg of the molecule with respect to the control group, see Fig. 6.

Example 4. Antibiofilm activity.-

[0063]

Strain	Resistance profile	MBIC formula (I) (mg/L)	MBIC Ciprofloxacin (Cip) (mg/L)	MBIC Levofloxacin (Lvx) (mg/L)
MRSA 1	Cip, Cli, Eri, Pen, Lvx	1	256	>256
MRSA 2	Gen, Cip, Cli, Eri, Pen, Lvx	1	256	128
MRSA, methicillin resistant <i>S. aureus</i> ; Cip, ciprofloxacin; Cli, clindamycin; Eri, erythromycin; Pen, penicillin; Lvx, levofloxacin; Gen, gentamicin.				

[0064] This example evidenced the high antibiofilm activity shown by the compound of formula (I) in comparison with Cip and Lvx. The compounds are active at concentrations until 8-fold lower (MIC 256 mg/L for Cip in contrast to 1 mg/L for formula(I) compound) than these antimicrobial agents.

[0065] The above describes embodiments of the present invention.

[0066] The scope of the present invention is defined in the following set of claims.

REFERENCES CITED IN THE DESCRIPTION

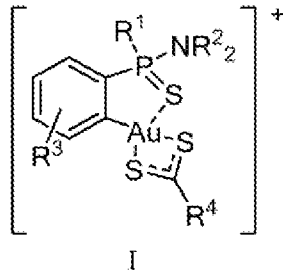
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Patentkrav

1. Guld(III)-kompleks med formelen (I):



5

hvor:

R^1 er valgt uafhængigt fra aryl og amin;

10

R^2 er valgt uafhængigt fra alkyl og cycloalkyl;

R^3 er valgt uafhængigt fra hydrogen, halogen, nitro, cyano, alkyl, alkyloxy, alkylamino, aminodialkyl, hydroxyalkyl, trialkylsilyl, aryldialkylsilyl, alkylthio, cycloalkyl, aryl, heterocyclus, polycyclus, aminosyre, peptid og carbonhydratderivat; og

15

R^4 er valgt uafhængigt fra alkyl, cycloalkyl, alkylalkoxy, alkylamino, dialkylamino, alkylthio, trialkylfosfino, dialkylarylfosfino, alkylarylfosfino, triarylfosfino, aryl, heterocyclus, polycyclus, aminosyre, peptid og carbonhydrat-derivat.

- 20 2. Guld(III)-komplekset ifølge krav 1, som desuden omfatter et kompleks med to type (I)-strukturer, der er forbundet af en piperazin-ring.

3. Guld(III)-komplekset ifølge krav 2, som desuden omfatter homo- og heterobinukleære komplekser af type (I), hvori R^4 har koordinationspositioner til et andet metal.

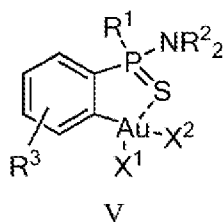
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4. Guld(III)-komplekset ifølge krav 1, hvori R^1 omfatter en fenyyl; R^2 omfatter en alkyl eller en cycloalkyl; R^3 omfatter en hydrogen; og R^4 omfatter en alifatisk amin.
- 5 5. Guld(III)-komplekset ifølge krav 4, hvori den alifatiske amin omfatter NMe_2 , NEt_2 , $N(CH_2Ph)_2$, pyrrolidyl-, piperidinyl- og azepanyl-kæder, eller heterocyklisk herunder piperazinyl eller morfolinyl.
6. Konjugatet, der omfatter guld(III)-komplekset ifølge ethvert af kravene 1 til 5 og
10 mindst én bærer, fortrinsvis en farmakologisk bærer.
7. En farmakologisk sammensætning, der omfatter guld(III)-komplekset ifølge ethvert af kravene 1 til 5 eller konjugatet ifølge krav 6, og mindst ét farmakologisk acceptabelt excipiens.
15
8. Guld(III)-komplekset ifølge ethvert af kravene 1 til 5, konjugatet ifølge krav 6 eller den farmakologiske sammensætning i krav 7 til dets brug som et lægemiddel.
- 20 9. Guld(III)-komplekset ifølge ethvert af kravene 1 til 5, konjugatet ifølge krav 6 eller den farmakologiske sammensætning i krav 7 til dets brug som et lægemiddel ved behandling og/eller forebyggelse af infektioner.
10. Guld(III)-komplekset ifølge ethvert af kravene 1 til 5, konjugatet ifølge krav 6
25 eller den farmakologiske sammensætning i krav 7 til dets brug som et lægemiddel ved behandling og/eller forebyggelse af bakteriel infektion.
11. Guld(III)-komplekset ifølge ethvert af kravene 1 til 5, konjugatet ifølge krav 6 eller den farmakologiske sammensætning i krav 7 til dets brug som et
30 lægemiddel ved behandling og/eller forebyggelse af bakteriel infektion, der er forårsaget af multiresistente bakterier.

12. Brug af guld(III)-komplekset ifølge ethvert af kravene 1 til 5, konjugatet ifølge krav 6 eller den farmakologiske sammensætning i krav 4 til at hæmme dannelsen eller udviklingen af en biofilm, til at eliminere modne biofilm og til at reducere biofilmens biomasse.

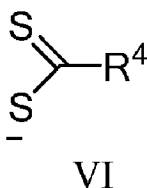
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13. Fremgangsmåde til forberedelse af guld(III)-komplekset ifølge krav 1, som omfatter skabelse af reaktion mellem en forbindelse med formlen (V)



10

og en forbindelse med formlen (VI)



- 15 og efterfølgende dannelse af et farmakologisk stabilt salt eller solvat af det resulterende kompleks gennem behandling med en organisk eller uorganisk syre eller deres tilsvarende salte, hvori:

- 20 X^1 er valgt uafhængigt fra halogen, hydroxid eller acetoxy;
 X^2 er valgt uafhængigt fra halogen, hydroxid eller acetoxy;
 R^1 er valgt uafhængigt fra aryl og amin;
 R^2 er valgt uafhængigt fra alkyl og cycloalkyl;
 R^3 er valgt uafhængigt fra hydrogen, halogen, nitro, cyano, alkyl, alkyloxy, alkylamino, aminodialkyl, hydroxyalkyl, trialkylsilyl, aryldialkylsilyl,
 25 alkylthio, cycloalkyl, aryl, heterocyclus, polycyclus, aminosyre, peptid og carbonhydratderivat; og

R^4 er valgt uafhængigt fra alkyl, cycloalkyl, alkylalkoxy, alkylamino, dialkylamino, alkylthio, trialkylfosfino, dialkylarylfosfino, alkyl diarylfosfino, triarylfosfino, aryl, heterocyclus, polycyclus, aminosyre, peptid og carbonhydrat-derivat.

5

14. Fremgangsmåden ifølge krav 13, som desuden omfatter inkludering af et kompleks med to type (I)-strukturer, der er forbundet med en piperazin-ring og homo- og heterobinukleære komplekser af type (I), hvori R^4 har koordinationspositioner til et andet metal.

10

15. Fremgangsmåden ifølge krav 13 eller 14, hvori R^1 omfatter en fenyl; R^2 omfatter en alkyl eller en cycloalkyl; R^3 omfatter en hydrogen; og R^4 omfatter en alifatisk amin.

DRAWINGS

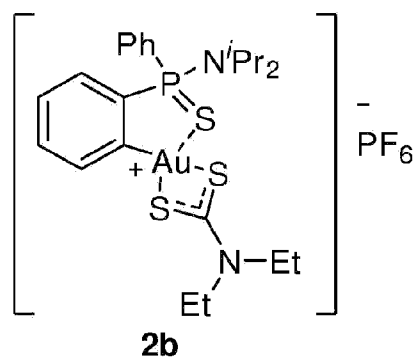


Fig. 1

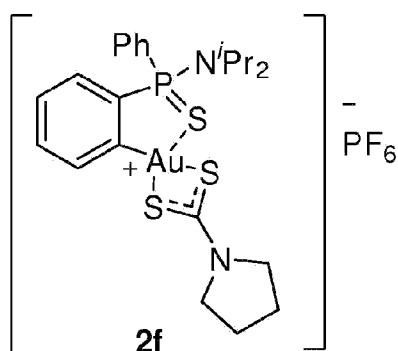


Fig. 2

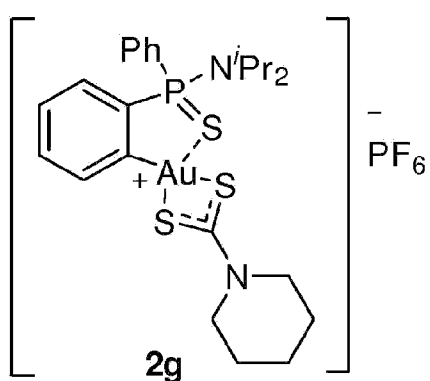


Fig. 3

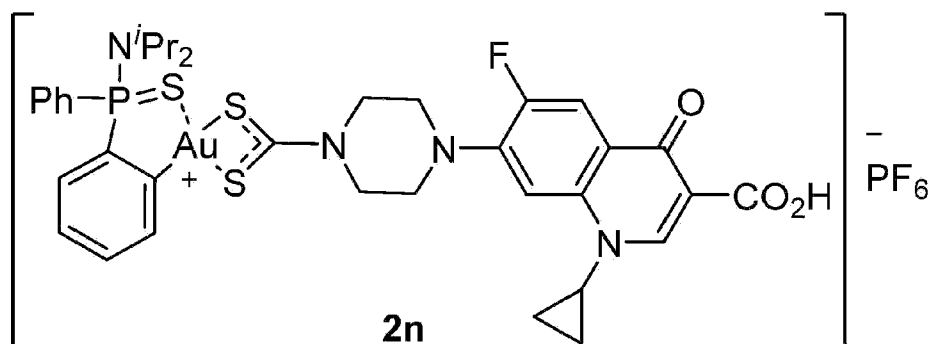


Fig. 4

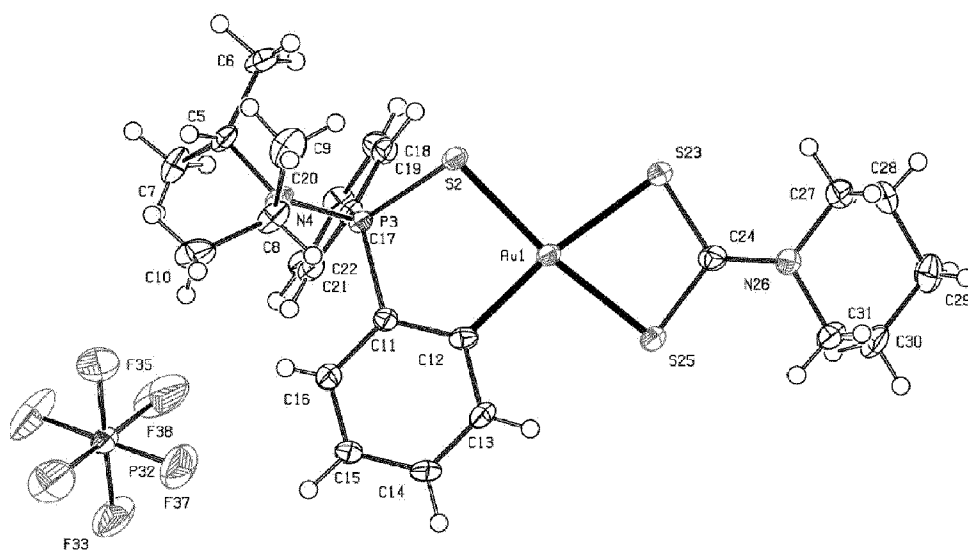


Fig. 5

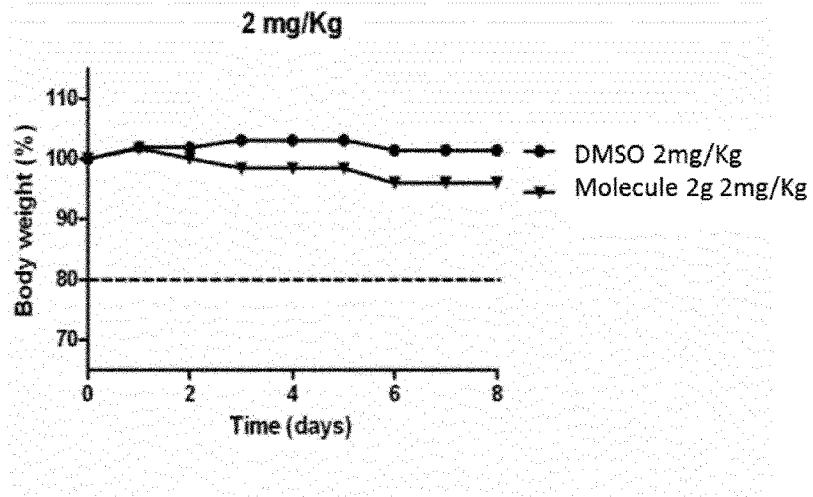


Fig. 6

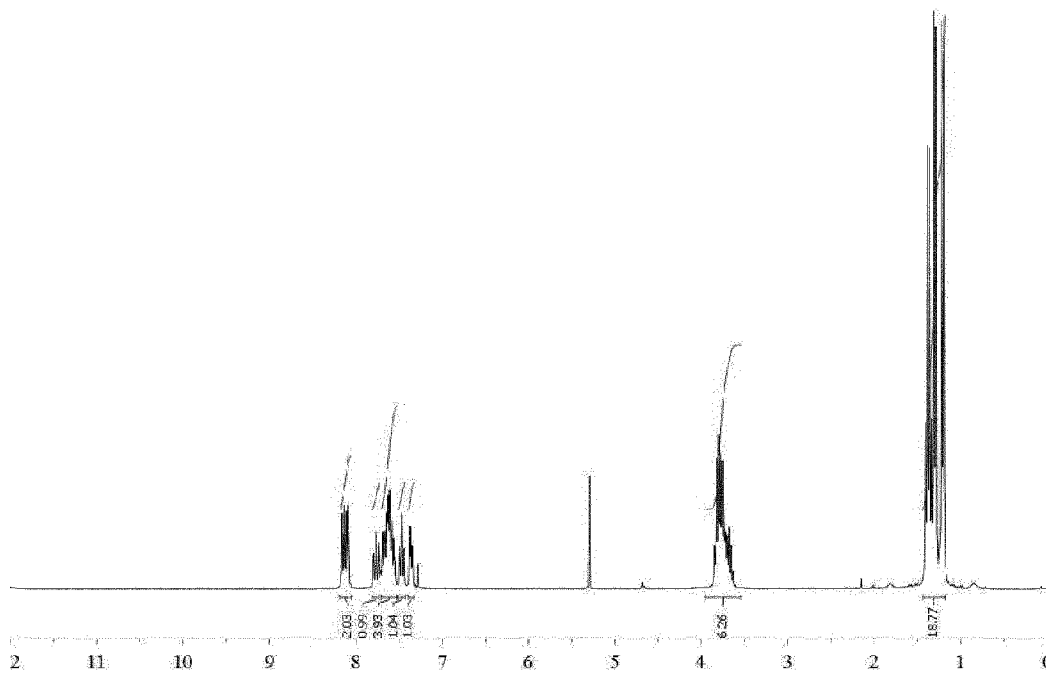


Fig. 7

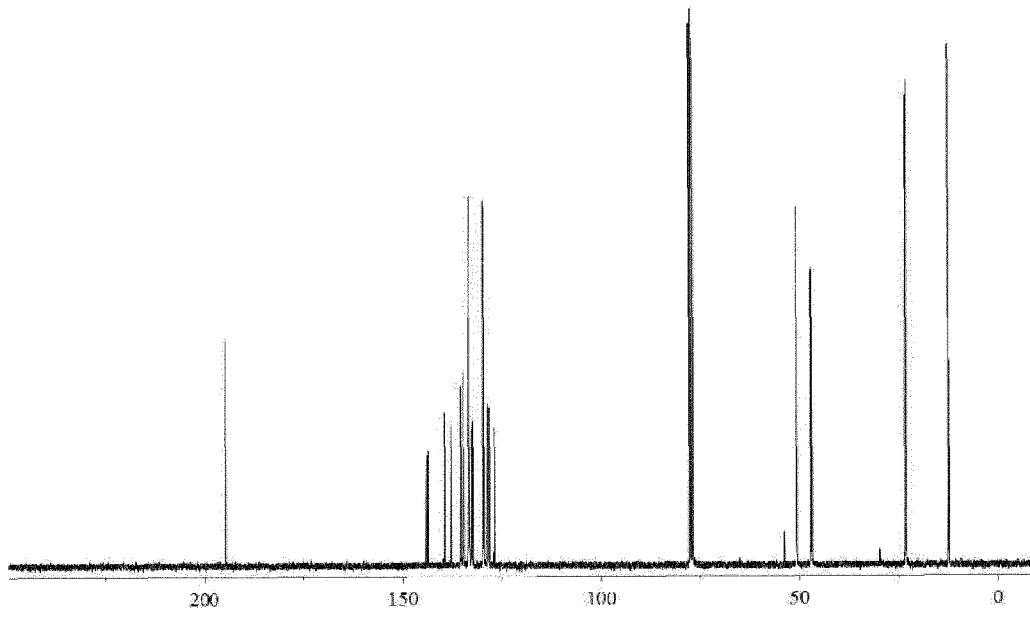


Fig. 8

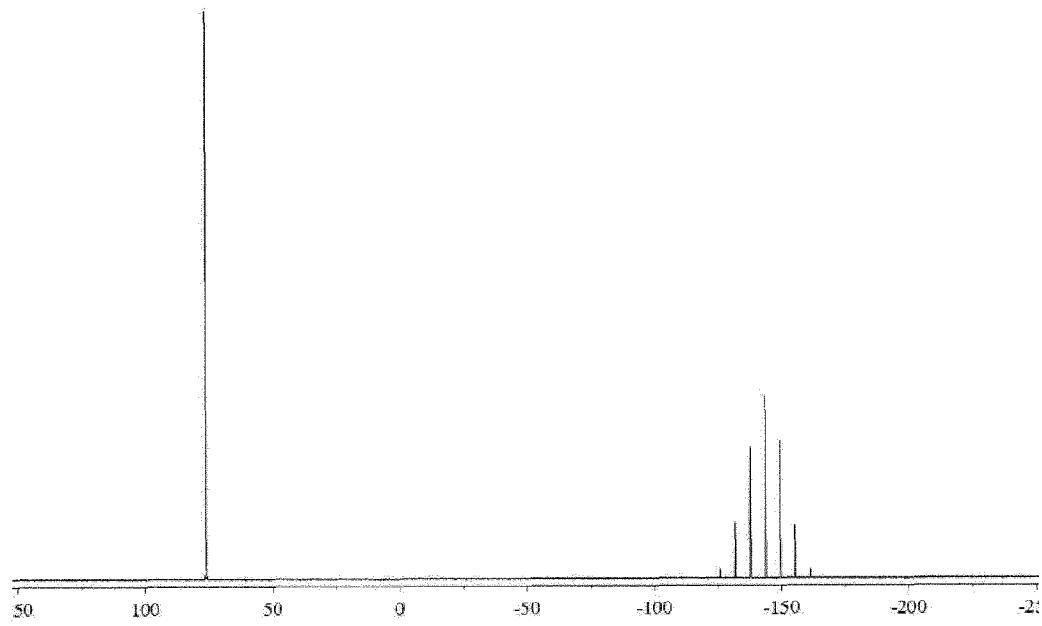


Fig. 9

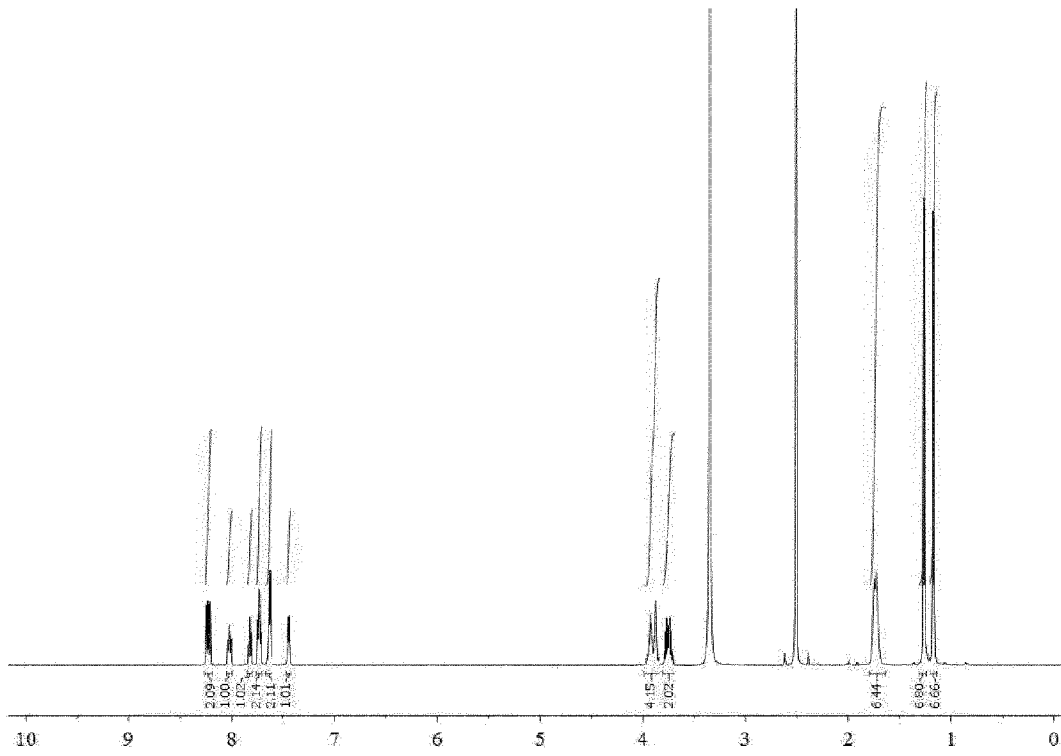


Fig. 10

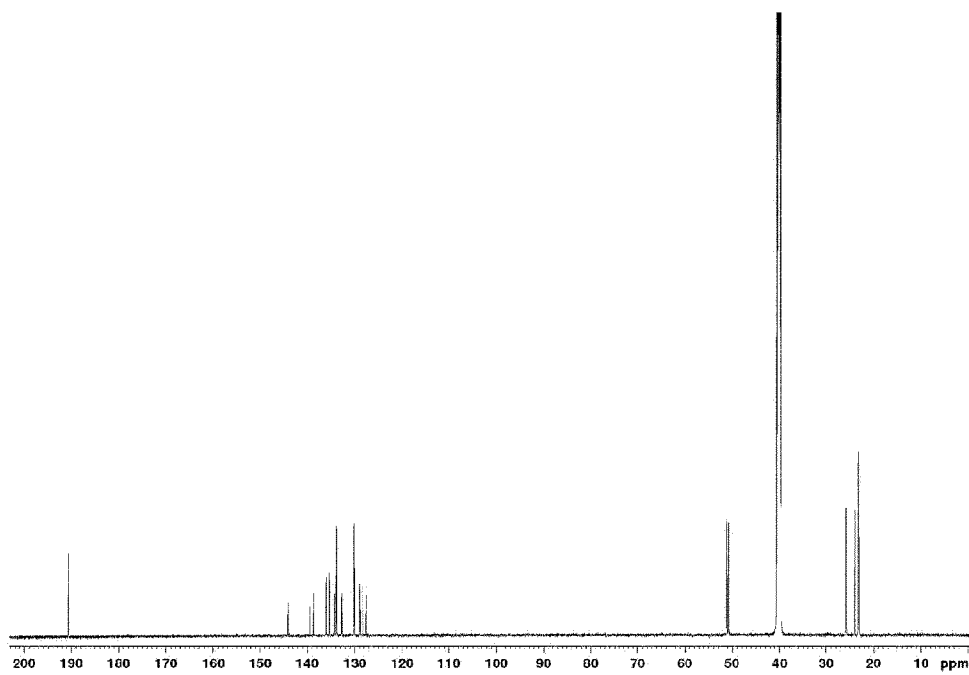


Fig. 11

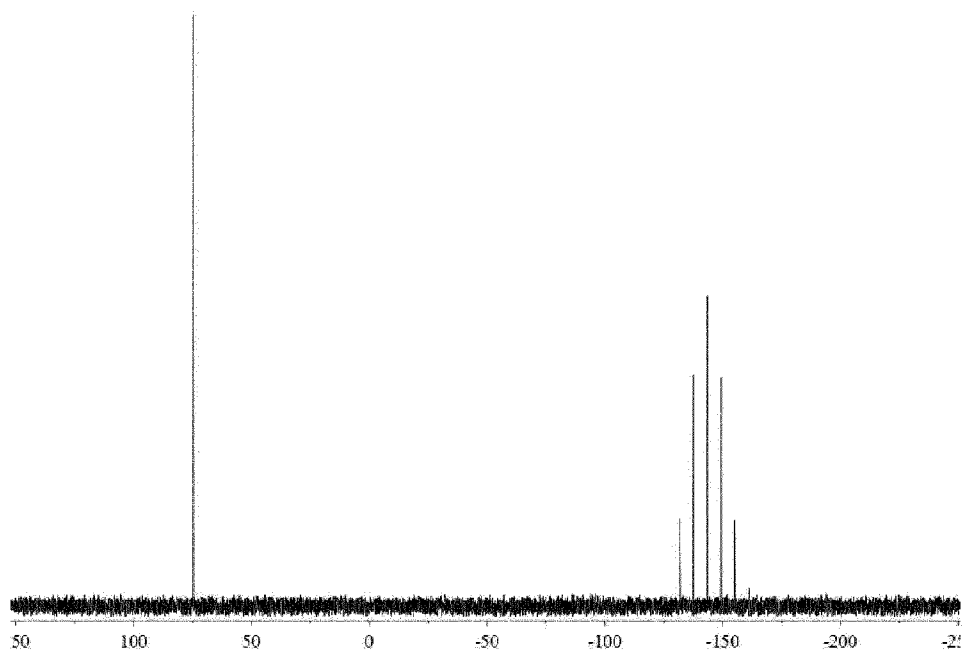


Fig. 12

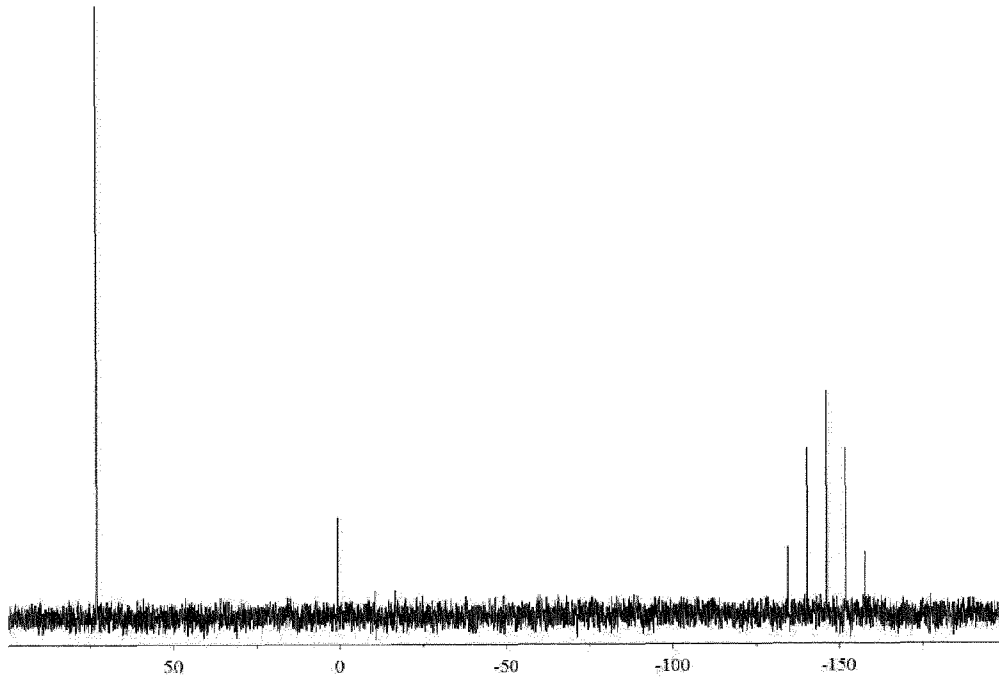


Fig. 13

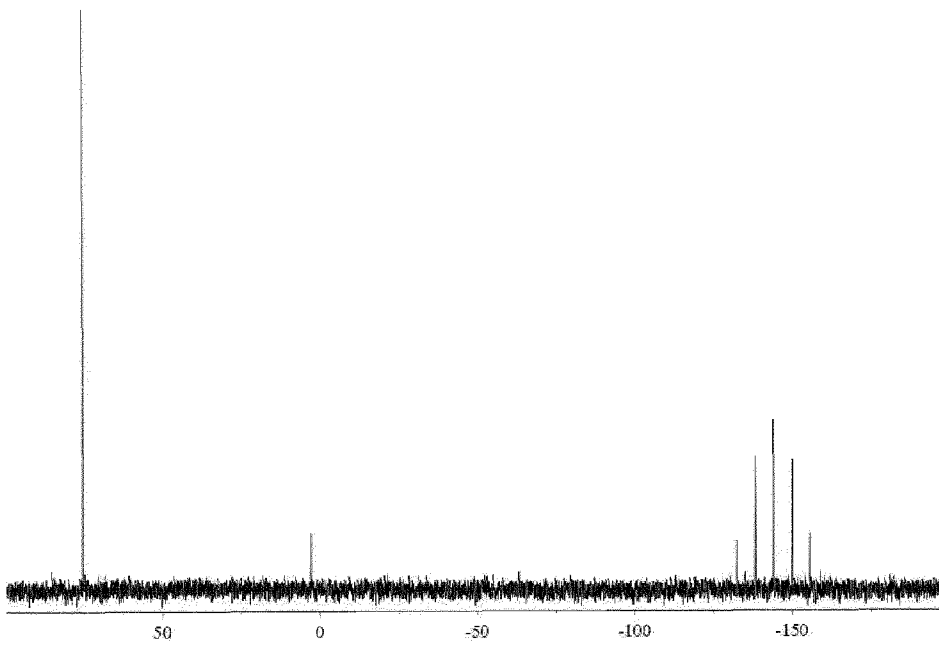


Fig. 14

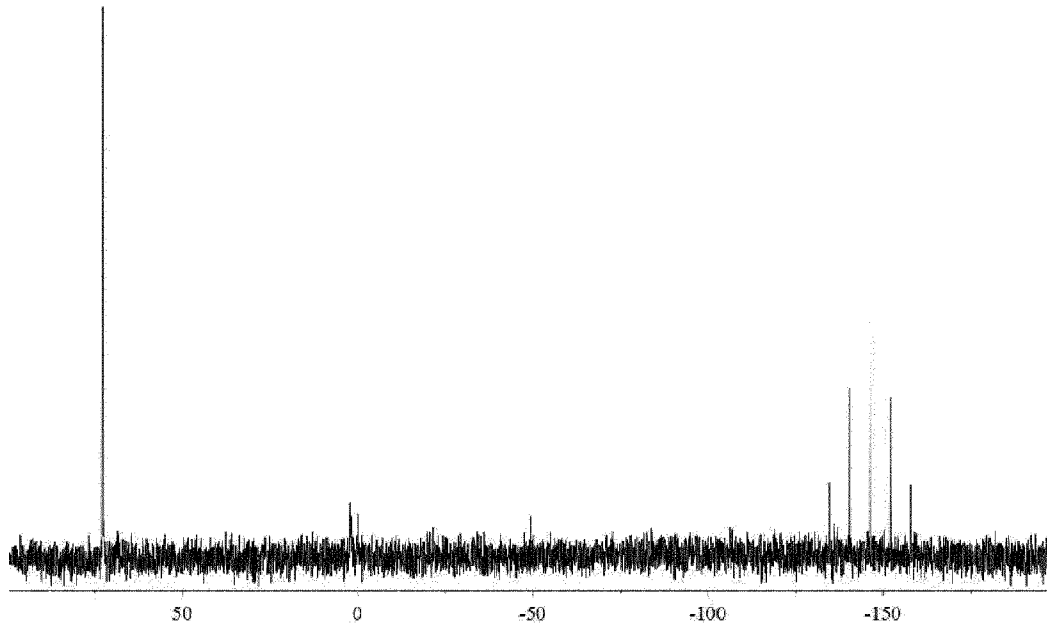


Fig. 15

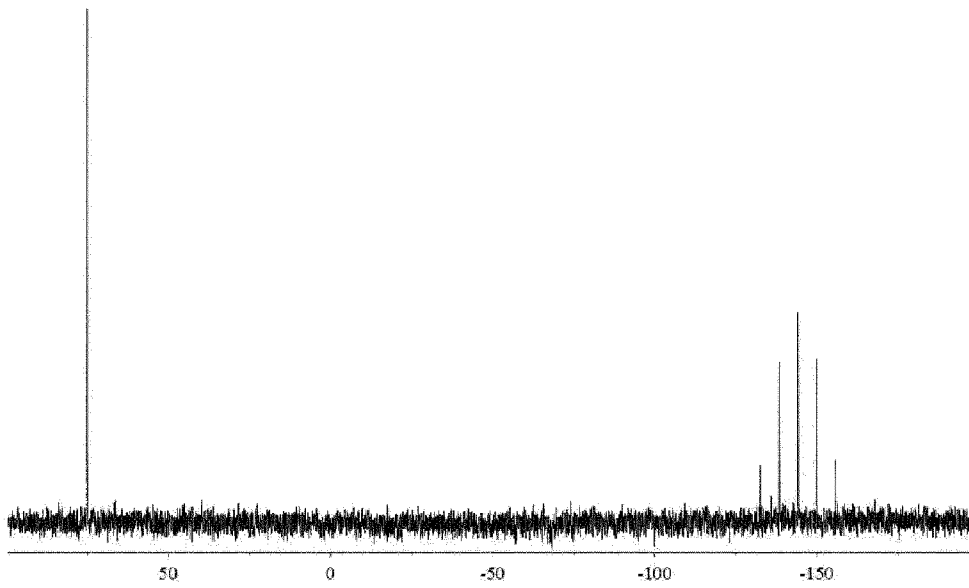


Fig. 16

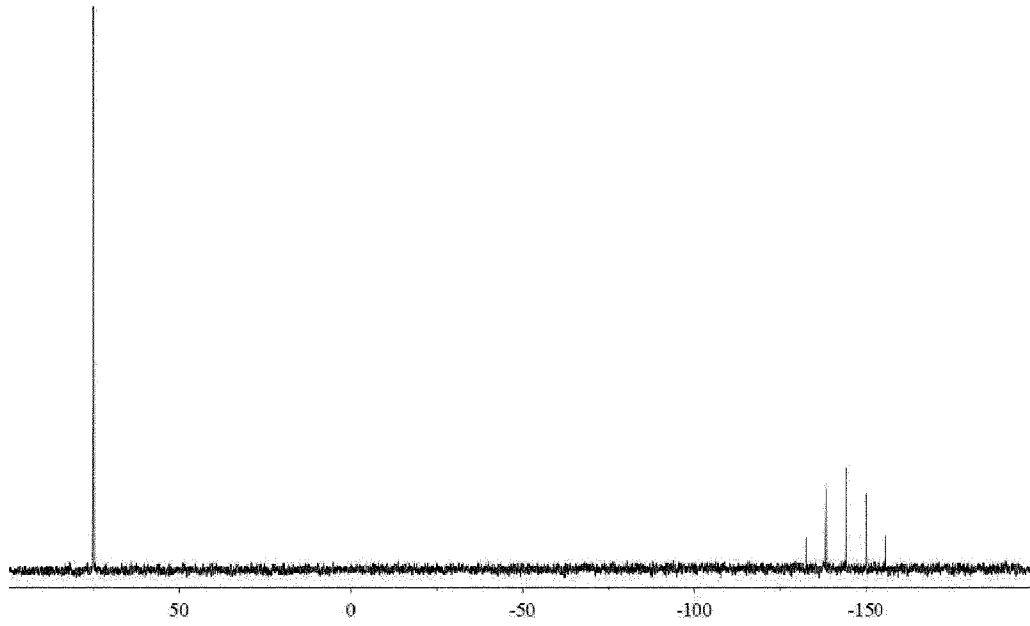


Fig. 17