| Title | PHARMACEUTICAL COMPOSITION CONTAINING CYCLOMETALATED N-HETEROCYCLIC CARBENE COMPLEXES FOR CANCER TREATMENT |
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Title: PHARMACEUTICAL COMPOSITION CONTAINING CYCLOMETALATED N-HETEROCYCLIC CARBENE COMPLEXES FOR CANCER TREATMENT

Abstract: The present invention discloses a pharmaceutical composition for treating cancers, comprising a cyclometalated N-heterocyclic carbene complex. Said cyclometalated N-heterocyclic carbene complex contains a gold (III) or platinum (II) atom. The pharmaceutical composition possesses anti-cancer activity such as the induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase.
PHARMACEUTICAL COMPOSITION CONTAINING CYCLOMETALATED N-HETEROCYCLIC CARBENE COMPLEXES FOR CANCER TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to provisional application Serial No. 61/255,667, filed on October 28, 2009 and to provisional application Serial No. 61/301,752, filed on February 5, 2010, both of which are incorporated herein by reference.

TECHNICAL FIELD

Described herein are pharmaceutical compositions containing a cyclometalated N-heterocyclic carbene complex, methods of making cyclometalated N-heterocyclic carbene complexes, and methods of using the cyclometalated N-heterocyclic carbene complexes including the treatment of cancer.

BACKGROUND

The success of cisplatin and its derivatives as anticancer agents has stimulated the development of metal-based compounds, including that of platinum and gold, for anticancer treatment [L. Kelland, Nat. Rev. Cancer 2007, 7, 573; C. F. Shaw III, Chem. Rev. 1999, 99, 2589]. In this context, extensive investigations on the biological properties of platinum(II), gold(I) and gold(III) have been reported. However, the development of the metal-based, particularly gold(III), as potential anti-cancer agents has been hampered by their poor stability in solution [M. Coronello, E. Mini, B. Caciagli, M. A. Cinellu, A. Bindoli, C. Gabbiani, L. Messori, J. Med. Chem. 2005, 48, 6761]. To our knowledge, very few cytotoxic gold(III) compounds such as [Au(bipy^c^-H)(OH)][PF_6] (bipy^c^-H = deprotonated 6-(1,1-dimethylbenzyl)-2,2'-bipyridine), [Au(dmamp)Cl_2] [dmamp = 2-(dimethylaminomethyl)phenyl], and gold(III) tetraarylporphyrins [C.-M. Che, R. W.-Y. Sun, W.-Y. Yu, C.-B. Ko, N. Zhu, H. Sun, Chem. Commun. 2003, 1718], have been reported to have significant stability.

The synthesis and photophysical properties of various cyclometalated gold(III) N-heterocyclic complexes have been reported by Yam et al [J. Am. Chem. Soc. 2009, 131, 9076; US 2009/0278453 A1]. Yet, the biological properties, notably the anti-cancer properties, of these complexes are completely unknown in the literature.

Cyclometalated platinum(II) complexes containing π-aromatic ligands have long been known to be metallointercalators for double-stranded DNA as the planar metal complex
cations can insert between DNA base pairs through ligand-ligand π-π stacking interactions [Chan, C. W.; Cheng, L. K.; Che, C. M. Coord. Chem. Rev. 1994, 132, 87]. Extensive studies have revealed that [PtII(terpy)(X)](X = chloride, 2-aminoethanethiolate, ethyl 2-mercaptoacetate, 2-hydroxyethanethiolate or cysteine), [PtII(NN)(en)](NN = 1,10-phenanthroline or 2,2’-bipyridine; en = ethylenediamine) and [PtII(CNN)(X)](CNN = 6-phenyl-2,2’-bipyridine, X = pyridine, 4-aminoypyridine or NN’-bis(isonicotinyl)-1,6-hexane-diamine) can intercalate DNA and display cytotoxic activities [(a) Howe-Grant, M.; Lippard, S. J. Biochemistry 1979, 18, 5762; (b) Lowe, G.; Droz, A. S.; Vilaivan, T.; Weaver, G. W.; Park, J. J.; Pratt, J. M.; Tweedale, L.; Kelland, L. R. J. Med. Chem. 1999, 42, 3167]. Platinum(II) complexes have other potential biological applications because they are usually kinetically stable, soluble in water and do not form insoluble hydrated oxides under physiological conditions. The tendency of square-planar platinum(II) complexes to form one-dimensional columnar stacks in their crystal structures and the aromaticity and size of chelating aromatic ligand such as terpy, NN or CNN all contribute to the ability of platinum(II) complexes to bind to DNA by intercalation.

The chemistry of N-heterocyclic carbene (NHC) has long been confined to metal coordination complexes derived from azolium compounds, which was started by Öfele and Wanzlick in 1968. In 1991, Arduengo successfully synthesized stable free NHCs, which had subsequently been used as ligands for transition metal complexes [Arduengo, A. J. III; Kline, M.; Calabrese, J. C.; Davidson, F. J. Am. Chem. Soc. 1991, 113, 9704]. Since then, many transition metal carbene complexes have been reported [Herrmann, W. A.; Köcher, C. Angew. Chem. Int. Ed. Engl. 1998, 36, 2162. (b) Bourissou, D.; Olivier, G.; Francois, P. G.; Bertrand, G Chem. Rev. 2000, 100, 39]. A leading motive is the advantage of NHC as ligand in the development of organometallic catalysts, whereas NHC ligands extend the scope of applications reached by phosphanes (functionalized, chiral, water-soluble, and immobilized derivatives). Metal-NHC complexes are usually stable to heat, air, and moisture [Herrmann, W. A.; Goossen, L. J.; Spigler, M. Organometallics. 1998, 17, 2162], and the coordination of carbene ligand to metal ion can be performed under simple and mild conditions. This feature stimulates a surge of interest, and many transition metal complexes containing NHC ligands derived from imidazolium ions have been synthesized [Herrmann, W. A.; Köcher, C. Angew. Chem. Int. Ed. Engl. 1997, 96, 2162]. Metal-N-heterocyclic carbene complexes have been used as catalysts for a spectrum of catalytic reactions, including Heck, Suzuki, and Kumada coupling reactions, alkene metathesis, and hydrosilylation [Huang, J.; Nolan, S. P. J. Am. Chem. Soc. 1999, 121, 9889]. In general, NHC ligands are accessible and their strong σ-donating character resemble to that of phosphine ligands [Herrmann, W. A.; Köcher, C. Angew. Chem. Int. Ed. Engl. 1997, 96, 2162]. In literature, however, there are few PtII-NHC complexes [(a) Unger, Y.; Zeller, A.; Ahrens, S.; Strassner, T. Chem. Commun. 2008, 3263.
SUMMARY

The following presents a simplified summary of the invention in order to provide a basic understanding of some aspects of the invention. This summary is not an extensive overview of the invention. It is intended to neither identify key or critical elements of the invention nor delineate the scope of the invention. Rather, the sole purpose of this summary is to present some concepts of the invention in a simplified form as a prelude to the more detailed description that is presented hereinafter.

Described herein is directed to a pharmaceutical composition for treatment of cancer comprising a cyclometalated N-heterocyclic carbene complex.

In one embodiment, a method for cancer treatment resulting in induction of cell death, inhibition of cellular proliferation, or inhibition of topoisomerase comprises administering in need thereof a composition comprising an effective amount of a cyclometalated carbene complex. The cyclometalated carbene complex is a gold(III) or platinum(II) complex described herein can be represented by one or more structural formulae of I, II, III or IV:
or a pharmaceutically acceptable salt thereof, wherein,

- M is selected from the metal ion of Au$^{3+}$ or Pt$^{2+}$;

- X is selected from a carbon atom or a nitrogen atom;

- $R_1$, $R_8$, $R_{13}$, $R_{18}$, $R_{26}$, and $R_{29}$ are each independently selected from the group consisting of -H, and

- $R_2$, $R_3$, $R_4$, $R_5$, $R_9$, $R_{10}$, $R_{14}$, $R_{15}$, $R_{16}$, $R_{17}$, $R_{19}$, $R_{20}$, $R_{21}$, $R_{22}$, $R_{27}$, $R_{28}$, $R_{31}$, and $R_{32}$ are each independently selected from the group consisting of -H and -NO$_2$; or each pair of $R_2$ and $R_3$, $R_4$ and $R_5$, $R_9$ and $R_{10}$, $R_{14}$ and $R_{15}$, $R_{16}$ and $R_{17}$, $R_{19}$ and $R_{20}$, $R_{21}$ and $R_{22}$, $R_{27}$ and $R_{28}$, $R_{31}$ and $R_{32}$ is independently joined together to form

- $R_6$, $R_7$, $R_{11}$, $R_{12}$, $R_{23}$, $R_{24}$, $R_{32}$ and $R_{33}$ are each independently selected from the group consisting of -CH$_3$, -C$_2$H$_5$, -C$_3$H$_7$, -C$_4$H$_9$, -CH$_2$OH, -C$_2$H$_5$OH, -C$_3$H$_6$OH, -C$_4$H$_8$OH, and

- $R_{25}$ and $R_{34}$ are each independently selected from the group consisting of -CH$_2$-, -C$_2$H$_4$-, -C$_3$H$_6$- and -C$_4$H$_8$-;
- Each A is independently a pharmaceutically acceptable counter-ion;

- \( n \) is an integer ranging from 0 to +4;

- \( b \) is an integer ranging from -4 to -1;

- \( y \) is equal to the absolute value of \( n/b \) when \( n > 0 \); and

- \( yA^b \) is absence when \( n \) is equal to 0.

These gold(III) and platinum(II) complexes are stable in air and physiological conditions and display higher anti-cancer activity than the clinically used cisplatin. In addition, the ease of syntheses and structural modification also helps these complexes for prevalent clinical applications.
BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows chemical structures of the gold-based cyclometalated N-heterocyclic carbene complexes (complexes 1–10) in accordance with the present invention.

Fig. 2 shows chemical structures of the platinum-based cyclometalated N-heterocyclic carbene complexes (complexes 11–25) in accordance with the present invention.

Fig. 3 shows the *in vivo* anti-cancer properties of complex 1 and complex 14.

Fig. 4 shows the topoisomerase I-mediated relaxation of supercoiled DNA by complexes 1, 2, 3 and CPT.

Fig. 5 shows the molecular modeling of complex 1 interacting with topoisomerase I-DNA. The topoisomerase I is in the ribbon representation and colored in yellow, while DNA is colored in green and is in a ball and stick model of complex 1.
Detailed Description

Disclosed are pharmaceutical compositions for treatment of cancer comprising a Group 10 or 11 transition metal cyclometalated N-heterocyclic carbene complex, such as a gold(III) (or Au(III) or Au$_{3}^{3+}$) cyclometalated N-heterocyclic carbene complex or a platinum(II) (or Pt(II) or Pt$_{2}^{2+}$) cyclometalated N-heterocyclic carbene complex. A pharmaceutical composition can contains at least one cyclometalated N-heterocyclic carbene complex in amount effective for an anti-cancer activity such as the induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase.

As noted herein, “cyclometalated N-heterocyclic carbene complex” refers to a molecule of a platinum(II) or a gold(III) ion connected to a tridentate ligand and a N-heterocyclic carbene ligand, which can be represented by structural formulae I, II, III or IV, or a pharmaceutically acceptable salt thereof:
or a pharmaceutically acceptable salt thereof, wherein,
- M is selected from the metal ion of Au\(^{3+}\) or Pt\(^{2+}\);

- X is selected from a carbon atom or a nitrogen atom;

- \(R^1, R^8, R^{13}, R^{16}, R^{26}\), and \(R^{29}\) are each independently selected from the group

\[
\begin{align*}
\text{consisting of } & -\text{H}, \\
& \text{and } \end{align*}
\]

- \(R^2, R^3, R^4, R^5, R^9, R^{10}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, R^{22}, R^{27}, R^{28}, R^{31}\), and \(R^{32}\) are each independently selected from the group consisting of \(-\text{H}\) and \(-\text{NO}_2\); or each pair of \(R^2\) and \(R^3\), \(R^4\) and \(R^5\), \(R^9\) and \(R^{10}\), \(R^{14}\) and \(R^{15}\), \(R^{16}\) and \(R^{17}\), \(R^{19}\) and \(R^{20}\), \(R^{21}\) and \(R^{22}\), \(R^{27}\) and \(R^{28}\), \(R^{31}\) and \(R^{32}\) is independently joined together to form

\[
\begin{align*}
& \text{or } \\
& \end{align*}
\]

- \(R^6, R^7, R^{11}, R^{12}, R^{23}, R^{24}, R^{32}\) and \(R^{33}\) are each independently selected from the group consisting of \(-\text{CH}_3\), \(-\text{C}_2\text{H}_5\), \(-\text{C}_3\text{H}_7\), \(-\text{C}_4\text{H}_9\), \(-\text{CH}_2\text{OH}\), \(-\text{C}_2\text{H}_5\text{OH}\), \(-\text{C}_3\text{H}_6\text{OH}\), \(-\text{C}_4\text{H}_8\text{OH}\), \(\text{and } \end{align*}

- \(R^{25}\) and \(R^{34}\) are each independently selected from the group consisting of \(-\text{CH}_2\), \(-\text{C}_2\text{H}_4\), \(-\text{C}_3\text{H}_6\) and \(-\text{C}_4\text{H}_8\).
- Each A is independently a pharmaceutically acceptable counter-ion;
- n is an integer ranging from 0 to +4;
- b is an integer ranging from -4 to -1;
- y is equal to the absolute value of n/b when n is >0; and
- yA^b is absence when n is equal to 0.

As used herein, the term “tridentate ligand” refers to a di-anionic substituted/non-substituted 2,6-diphenylpyridine (hereinafter CNC) ligand or a mono-anionic substituted/non-substituted 6-phenyl-2,2'-bipyridine (hereinafter CNN) ligand. Non-limiting examples of the CNC ligands are:
non-limiting examples of the CNN ligands are:
As used herein, the term "N-heterocyclic carbene" refers to a ligand having one of the following chemical structures:

\[
\begin{align*}
\text{R}^1 & \text{N} & \text{N} & \text{R}^2, \\
\text{or} \\
\text{R}^1 \text{N} & \text{N} & \text{R}^5 & \text{N} & \text{N} & \text{R}^2
\end{align*}
\]

wherein:

\(\text{R}^1\) and \(\text{R}^2\) are each independently selected from the group consisting of alkyl having 1 to 5 carbon atoms such as \(-\text{CH}_3, -\text{C}_2\text{H}_5, -\text{C}_3\text{H}_7, -\text{C}_4\text{H}_9\), alkanol having 1 to 5 carbon atoms such as \(-\text{CH}_2\text{OH}, -\text{C}_2\text{H}_4\text{OH}, -\text{C}_3\text{H}_6\text{OH}, -\text{C}_4\text{H}_8\text{OH}\), substituted benzyl such as

\[
\text{and}
\]


$R^5$ is selected from the group consisting of alkyl having 1 to 5 carbon atoms such as -\text{CH}_2-, -\text{C}_2\text{H}_4-, -\text{C}_3\text{H}_6-, and -\text{C}_4\text{H}_8-. In one embodiment, the N-heterocyclic carbene is coordinated with the gold(III) or platinum(II) ion.

It will be understood that the di-anionic CNC ligand or the mono-anionic CNN ligand can form a non-neutral complex with the gold(III) or the platinum(II) ion. For instance, the net positive charge on the gold(III) or the platinum(II) ion can be greater than the absolute net negative charge of the CNC or the CNN ligand. In view of this, there can be at least one counter-anion coordinated to the cyclometalated N-heterocyclic carbene complex for charge neutralization. Accordingly, the phrase “pharmaceutically acceptable salt,” as used herein, includes salts formed from charged cyclometalated N-heterocyclic carbene complex and counter-anion(s).

In one embodiment of the cyclometalated N-heterocyclic carbene complex, $n$ is an integer selected from 1, 2, 3 and 4.

As used herein, the phrase “counter-anion” refers to an ion associated with a positively charged cyclometalated N-heterocyclic carbene complex. Non-limiting examples of counter-ions include halogens such as fluoride, chloride, bromide, iodide; sulfate; phosphate; trifluoromethanesulfonate; acetate; nitrate; perchlorate; acetylacetonate; hexafluorophosphate and hexafluoroacetylacetonate.

In one embodiment, the structure of the cyclometalated N-heterocyclic carbene complex can be either in monomeric (formulae I and II) or dimeric (formulae III and IV) form. Also, the cyclometalated N-heterocyclic carbene complex can exist as a single molecule or aggregated molecules (an agglomerate).

As used herein, the phrase of “pharmaceutically acceptable carrier” means a carrier or combination of carrier ingredients approved by a regulatory agency of the Federal or a state government or listed in the U. S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, mammals, and more particularly in humans. Non-limiting examples of pharmaceutically acceptable carriers include liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin. Water is a frequently used when the compound of the invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions.

As noted above, the present invention relates to a pharmaceutical composition for
cancer treatment.

In one embodiment, the invention relates to a pharmaceutical for cancer treatment by induction of cell death (including but not limited to apoptosis) of cancer cells comprising administering with a responsive form of cancer a composition comprising an effective amount of one or more cyclometalated N-heterocyclic carbene complexes.

In another embodiment, the invention relates to a pharmaceutical for cancer treatment by inhibition of the proliferation of cancer cells comprising administering with a responsive form of cancer a composition comprising an effective amount of one or more cyclometalated N-heterocyclic carbene complexes.

In another embodiment, the invention relates to a pharmaceutical for cancer treatment by inhibition of topoisomerase or poisoning of topoisomerase comprising administering with a responsive form of cancer a composition comprising an effective amount of one or more cyclometalated N-heterocyclic carbene complexes.

The cyclometalated N-heterocyclic carbene complexes of this invention can be represented by one or more of structural formulae I, II, III or IV, or a pharmaceutically acceptable salt thereof:
or a pharmaceutically acceptable salt thereof, wherein,
- M is selected from the metal ion of Au\(^{3+}\) or Pt\(^{2+}\);
- X is selected from a carbon atom or a nitrogen atom;
- \(R^1, R^8, R^{13}, R^{18}, R^{26}, \) and \(R^{29}\) are each independently selected from the group consisting of -H, \(\circ\circ\) and ;
- \(R^2, R^3, R^4, R^9, R^{10}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, R^{22}, R^{27}, R^{28}, R^{31}, \) and \(R^{32}\) are each independently selected from the group consisting of -H and –NO\(_2\); or each pair of \(R^2\) and \(R^3\), \(R^4\) and \(R^5\), \(R^9\) and \(R^{10}\), \(R^{14}\) and \(R^{15}\), \(R^{16}\) and \(R^{17}\), \(R^{19}\) and \(R^{20}\), \(R^{21}\) and \(R^{22}\), \(R^{27}\) and \(R^{28}\), \(R^{31}\) and \(R^{32}\) is independently joined together to form or ;
- \(R^6, R^7, R^{11}, R^{12}, R^{23}, R^{24}, R^{32}\) and \(R^{33}\) are each independently selected from the group consisting of -CH\(_3\), -C\(_2\)H\(_5\), -C\(_3\)H\(_7\), -C\(_4\)H\(_9\), -CH\(_2\)OH, -C\(_2\)H\(_4\)OH, -C\(_3\)H\(_6\)OH, -C\(_4\)H\(_8\)OH, and ;
- \(R^{25}\) and \(R^{34}\) are each independently selected from the group consisting of -CH\(_2\)-, -C\(_2\)H\(_4\)-, -C\(_3\)H\(_6\)- and -C\(_4\)H\(_8\)-;
- Each A is independently a pharmaceutically acceptable counter-ion;
- n is an integer ranging from 0 to +4;
- b is an integer ranging from -4 to -1;
- y is equal to the absolute value of n/b when n is >0; and
- yA^b is absence when n is equal to 0.

In one embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Au^{3+};
- X is a carbon atom;
- R^1, R^2, R^3, R^4, and R^5 are each -H;
- R^6 and R^7 are each -CH₃;
- A is a OSO₂CF₃ anion;
- n is +1;
- b is -1; and
- y is 1 (complex I).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- M is Au^{3+};
- X is a carbon atom;
- R^{13} and R^{18} are each -H;
- R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21} and R^{22} are each -H;
- R^{23} and R^{24} are each -C₄H₉;
- R^{25} is -CH₂-;
- A is a OSO₂CF₃ anion;
- n is +2;
- b is -1; and
- y is 2 (complex 2).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- M is Au$^{3+}$;
- X is a carbon atom;
- R$^{13}$ and R$^{18}$ are each -H;
- R$^{14}$, R$^{15}$, R$^{16}$, R$^{17}$, R$^{19}$, R$^{20}$, R$^{21}$ and R$^{22}$ are each -H;
- R$^{23}$ and R$^{24}$ are each -C$_4$H$_9$;
- R$^{25}$ is -C$_2$H$_4$-;
- A is a OSO$_2$CF$_3$ anion;
- n is +2;
- b is -1; and
- y is 2 (complex 3).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Au$^{3+}$;
- X is a carbon atom;
- R$^1$, R$^2$, R$^3$, R$^4$, and R$^5$ are each -H;
- R$^6$ and R$^7$ are each

\[
\text{[Diagram]}
\]
- A is a OSO$_2$CF$_3$ anion;
- n is +1;
- b is -1; and
- y is 1 (complex 4).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition
of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Au\(^{3+}\),
- X is a carbon atom;
- R\(^1\), R\(^2\), R\(^3\), R\(^4\), and R\(^5\) are each \(-\)H;
- R\(^6\) is
- R\(^7\) is
- A is a OSO\(_2\)CF\(_3\) anion;
- n is +1;
- b is -1; and
- y is 1 (complex 5).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula II or a pharmaceutically acceptable salt thereof, wherein,
- M is Au\(^{3+}\),
- X is a carbon atom;
- R\(^8\) is
- R\(^9\) and R\(^10\) are each \(-\)H;
- R\(^11\) and R\(^12\) are each \(-\)CH\(_3\);
- A is a OSO\(_2\)CF\(_3\) anion;
- n is +1;
- b is -1; and
- y is 1 (complex 6).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a
cyclometalated N-heterocyclic carbene complex of formula IV or a pharmaceutically acceptable salt thereof, wherein,

- \( M \) is \( \text{Au}^{3+} \);
- \( X \) is a carbon atom;

- \( R^{26} \) and \( R^{29} \) are each ;
- \( R^{27}, R^{28}, R^{30} \) and \( R^{31} \) are each -H;
- \( R^{32} \) and \( R^{33} \) are each -C\(_4\)H\(_9\);
- \( R^{34} \) is -CH\(_2\)-;
- \( A \) is a OSO\(_2\)CF\(_3\) anion;
- \( n \) is +2;
- \( b \) is -1; and
- \( y \) is 2 (complex 7)

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,

- \( M \) is \( \text{Au}^{3+} \);
- \( X \) is a carbon atom;

- \( R^{1} \) is ;

- each pair of \( R^{2} \) and \( R^{3} \), and \( R^{4} \) and \( R^{5} \) is joined together to form ;
- \( R^{6} \) and \( R^{7} \) are each -CH\(_3\);
- \( A \) is a OSO\(_2\)CF\(_3\) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 8).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a
cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- \( M \) is Au\(^{3+} \);
- \( X \) is a carbon atom;
- \( R^{13} \) and \( R^{18} \) are each
- each pair of \( R^{14} \) and \( R^{15} \), \( R^{16} \) and \( R^{17} \), \( R^{19} \) and \( R^{20} \), \( R^{21} \) and \( R^{22} \), is joined together to form
- \( R^{23} \) and \( R^{24} \) are each \(-C_4H_9\);
- \( R^{25} \) is \(-CH_2-\);
- \( A \) is a OSO\(_2\)CF\(_3\) anion;
- \( n \) is +2;
- \( b \) is -1; and
- \( y \) is 2 (complex 9).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoiso merase and/or poisoning of topoiso merase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula II or a pharmaceutically acceptable salt thereof, wherein,
- \( M \) is Au\(^{3+} \);
- \( X \) is a carbon atom;
- \( R^8 \) is
- \( R^9 \) is \(-NO_2\);
- \( R^{10} \) is \(-H\);
- \( R^{11} \) and \( R^{12} \) are each \(-CH_3\);
- \( A \) is a OSO\(_2\)CF\(_3\) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 10).
In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,

- M is Pt\(^{2+}\);
- X is a nitrogen atom;
- R \(^1\), R \(^2\), R \(^3\), R \(^4\), and R \(^5\) are each –H;
- R \(^6\) and R \(^7\) are each -CH\(_3\);
- A is a PF\(^6\) anion;
- n is +1;
- b is -1; and
- y is 1 (complex 11).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,

- M is Pt\(^{2+}\);
- X is a nitrogen atom;
- R \(^1\), R \(^2\), R \(^3\), R \(^4\), and R \(^5\) are each –H;
- R \(^6\) and R \(^7\) are each -C\(_2\)H\(_5\);
- A is a PF\(^6\) anion;
- n is +1;
- b is -1; and
- y is 1 (complex 12).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,

- M is Pt\(^{2+}\);
- X is a nitrogen atom;
- R \(^1\), R \(^2\), R \(^3\), R \(^4\), and R \(^5\) are each –H;
- R \(^6\) and R \(^7\) are each -C\(_3\)H\(_7\);
- A is a PF\(^6\) anion;
- n is +1;
- b is -1; and
- y is 1 (complex 13).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/ or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt^{2+};
- X is a nitrogen atom;
- R^1, R^2, R^3, R^4, and R^5 are each –H;
- R^6 and R^7 are each -C_6H_5;
- A is a PF^6 anion;
- n is +1;
- b is -1; and
- y is 1 (complex 14).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/ or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt^{2+};
- X is a nitrogen atom;
- R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are each –H;
- R^{23} and R^{24} are each -C_6H_5;
- R^{25} is -CH_2
- A is a PF^6 anion;
- n is +2;
- b is -1; and
- y is 2 (complex 15).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/ or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;
- $R^{13}$, $R^{14}$, $R^{15}$, $R^{16}$, $R^{17}$, $R^{18}$, $R^{19}$, $R^{20}$, $R^{21}$ and $R^{22}$ are each -H;
- $R^{23}$ and $R^{24}$ are each -C$_4$H$_9$;
- $R^{25}$ is -C$_3$H$_6$
- A is a PF$_6$ anion;
- n is +2;
- b is -1; and
- y is 2 (complex 16).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;

- $R^1$ is ;
- $R^2$, $R^3$, $R^4$, and $R^5$ are each -H;
- $R^6$ and $R^7$ are each -C$_3$H$_7$;
- A is a PF$_6$ anion;
- n is +1;
- b is -1; and
- y is 1 (complex 17).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;

- $R^1$ is ;
- \( R^2, R^3, R^4, \) and \( R^5 \) are each -H;
- \( R^6 \) and \( R^7 \) are each -C\(_3\)H\(_7\);
- \( A \) is a PF\(_6\) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 18).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- \( M \) is Pt\(^{2+}\);
- \( X \) is a nitrogen atom;
- \( R^{13} \) and \( R^{18} \) are each
- \( R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21} \) and \( R^{22} \) are each -H;
- \( R^{23} \) and \( R^{24} \) are each -C\(_4\)H\(_9\);
- \( R^{25} \) is -CH\(_2\);
- \( A \) is a PF\(_6\) anion;
- \( n \) is +2;
- \( b \) is -1; and
- \( y \) is 2 (complex 19).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- \( M \) is Pt\(^{2+}\);
- \( X \) is a nitrogen atom;
- \( R^{13} \) and \( R^{18} \) are each
- \( R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21} \) and \( R^{22} \) are each -H;
- \( R^{23} \) and \( R^{24} \) are each -C\(_4\)H\(_9\);
- $R^{25}$ is -CH$_2$
- $A$ is a PF$_6$ anion;
- $n$ is +2;
- $b$ is -1; and
- $y$ is 2 (complex 20).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- $M$ is Pt$^{2+}$;
- $X$ is a nitrogen atom;
- $R^1$ is -H;
- each pair of $R^2$ and $R^3$, and $R^4$ and $R^5$ is joined together to form 
- $R^6$ and $R^7$ are each -C$_3$H$_7$;
- $A$ is a PF$_6$ anion;
- $n$ is +1;
- $b$ is -1; and
- $y$ is 1 (complex 21).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula III or a pharmaceutically acceptable salt thereof, wherein,
- $M$ is Pt$^{2+}$;
- $X$ is a nitrogen atom;
- $R^{13}$ and $R^{18}$ are each -H;
- each pair of $R^{14}$ and $R^{15}$, $R^{16}$ and $R^{17}$, $R^{19}$ and $R^{20}$, and $R^{21}$ and $R^{22}$ is joined together to form 
- $R^2$ and $R^4$ are each -C$_4$H$_9$;
- $R^{25}$ is -CH$_2$
- $A$ is a PF$_6$ anion;
- n is +2;
- b is -1; and
- y is 2 (complex 22).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometallated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt²⁺;
- X is a nitrogen atom;
- R¹, R², R³, R⁴, and R⁵ are each -H;
- R⁶ is 

- R⁶ is -C₃H₆OH;
- A is a PF₆⁻ anion;
- n is +1;
- b is -1; and
- y is 1 (complex 23).

In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometallated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- M is Pt²⁺;
- X is a nitrogen atom;
- R¹, R² and R³ are each -H;

- R¹ and R² are joined together to form 

- R⁵ and R⁶ are each C₃H₇;
- A is a PF₆⁻ anion;
- n is +1;
- b is -1; and
- y is 1 (complex 24).
In another embodiment, the invention relates to a pharmaceutical composition for treatment of cancer by induction of cell death, inhibition of cellular proliferation, inhibition of topoisomerase and/or poisoning of topoisomerase comprising an effective amount of a cyclometalated N-heterocyclic carbene complex of formula I or a pharmaceutically acceptable salt thereof, wherein,
- \( M \) is \( \text{Pt}^{2+} \);
- \( X \) is a nitrogen atom;
- \( R^1, R^2 \) and \( R^3 \) are each -H;
- \( R^4 \) and \( R^5 \) are joined together to form \( \text{C}_4\text{H}_9 \);
- \( R^6 \) is \( \text{C}_4\text{H}_9 \);
- \( R^7 \) is -\( \text{C}_2\text{H}_4\text{OH} \);
- \( A \) is a PT\( ^6 \) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 25).

Methods of making the cyclometalated N-heterocyclic carbene complexes as described above generally involve reacting a cyclometalated complex with an N-heterocyclic carbene compound to form the cyclometalated N-heterocyclic carbene complex. In one embodiment, the cyclometalated N-heterocyclic carbene complexes are prepared by deprotonating a N-heterocyclic carbene compound and then reacting the deprotonated N-heterocyclic carbene compound with suitable cyclometalated complex comprising gold or platinum.

After the reaction, the cyclometalated N-heterocyclic carbene complexes are worked up and, if appropriate, purified by processes known to those skilled in the art. Typically, the workup and purification are effected by evaporation, filtration, extraction, column chromatography and/or recrystallization by processes known to those skilled in the art.
Examples

Example 1: Preparation and Characterization of the Cyclometalated N-Heterocyclic Carbene Complexes

Example 1 illustrates the synthesis and characterization of the gold(III)-based (Fig. 1) and the platinum(II)-based (Fig. 2) cyclometalated N-heterocyclic carbene complexes.

**Complex 1** Au(CNC)Cl (40.00 mg, 0.087 mmol), N,N′-dimethylimidazolium iodide (20.61 mg, 0.092 mmol) and KO'Bu (11.20 mg, 0.100 mmol) were refluxed in 25 mL CH₃CN overnight under an inert atmosphere. After 24 hours, a saturated LiOSO₂CF₃ solution in CH₃CN was added and the mixture was stirred at room temperature for another 30 minutes. The mixture was gravity filtered and the filtrate was collected. The filtrate was concentrated to about 5 mL, excess Et₂O was added and the mixture was kept <10 °C for 1 day. Pale yellow solid was formed. Yield: 49.32 mg, 82.6%. Anal. Calcd for C₂₃H₂₁N₅O₅F₃Au: C, 41.13; H, 2.83; N, 6.26. Found: C, 41.06; H, 3.01; N, 6.56. ¹H NMR (400 MHz, (CD₃)₂SO): δ 3.84 (s, 6H, -CH₃), 6.94 (d, 2H, J = 7.09 Hz), 7.31 (t, 2H, J = 6.70), 7.37 (t, 2H, J = 7.18), 7.83 (s, 2H), 7.99 (d, 2H, J = 7.51 Hz), 8.06 (d, 2H, J = 8.03), 8.25 (t, 1H, J = 8.01). ¹⁹F NMR (400 MHz, (CD₃)₂SO): δ -79.32. FAB-MS (+ve, m/z): 522 [M⁺].

**Complex 2**: Au(CNC)Cl (100 mg, 0.217 mmol), 1,1'-methylene bis(3-n-butylimidazolium) diiodide (56.20 mg, 0.109 mmol) and KO'Bu (25.80 mg, 0.230 mmol) were refluxed in 20 mL CH₃CN under an inert atmosphere overnight. A yellow colored solution was formed. The solution was treated in a similar manner to that of complex 1, yellow precipitates were crystallized out. Yield: 0.1081 g, 72.5%. Anal. Calcd for C₅₁H₄₆N₆O₆F₆S₂Au₂: C, 43.41; H, 3.29; N, 5.96. Found: C, 43.62; H, 3.33; N, 6.08. ¹H NMR (400 MHz, CD₃CN): δ 0.62 (t, 6H, J = 7.36, -²Bu), 1.03 (q, 4H, J = 7.53, -²²Bu), 1.62-1.66 (m, 4H, -²²Bu), 4.03 (t, 4H, J = 7.11, -²²Bu), 6.73 (d, 4H, J = 7.34), 6.83 (s, 2H), 6.91 (t, 4H, J = 7.39), 7.14 (t, 4H, J = 7.60), 7.41 (d, 4H, J = 7.73), 7.47 (d, 4H, J = 8.04), 7.69 (s, 2H), 8.02 (t, 2H, J = 8.02 Hz), 8.09 (s, 2H). ¹⁹F NMR (400 MHz, (CD₃)CN): δ -79.33. FAB-MS (+ve, m/z): 1261 [M + OSO₂CF₃⁺].

**Complex 3**: Au(CNC)Cl (100 mg, 0.217 mmol), 1,2-propylene bis (3-n-butylimidazolium) diiodide (57.73 mg, 0.109 mmol) and KO'Bu (25.80 mg, 0.230 mmol) were refluxed in 20 mL CH₃CN under an inert atmosphere overnight. A yellow colored solution was formed. The solution was treated in a similar manner to that of
complex 1, yellow precipitates were crystallized out. Yield: 0.1163 g, 78 %. Anal. Calcd for C$_{35}$H$_{50}$N$_6$O$_8$F$_6$S$_2$Au$_2$: C, 44.23; H, 3.50; N, 5.84. Found: C, 43.96; H, 3.49; N, 5.90. $^1$H NMR (400 MHz, CD$_3$CN): δ 0.69 (t, 6H, $J$ = 5.64, $^-$Bu), 1.13 (q, 4H, $^-$Bu), 1.66-1.67 (m, 4H, $^-$Bu), 2.43 (t, 2H, $J$ = 6.28), 4.04 (t, 4H, $J$=5.00), 4.19 (s, 4H), 6.83 (s, 4H), 7.14 (s, 4H), 7.23 (d, 4H, $J$ = 5.90), 7.47 (s, 4H), 7.69 (s, 4H), 7.74 (s, 4H), 8.14-8.15 (m, 2H). $^{19}$F NMR (400 MHz, CD$_3$CN): δ -79.311. ESI-Q-TOF-MS (+ve, m/z): 570 [M]$^{2+}$.

**Complex 4**: Synthesis similar to that of complex 1, by using Au(CNC)$_2$Cl (22.7 mg, 0.049 mmol), carbene (24.9 mg, 0.049 mmol) and KO'Bu (5.7 mg, 0.051 mmol). A pure brown solid was formed. Yield: 28.1 mg, 54.7 %. Anal. Calcd for C$_{51}$H$_{60}$N$_3$O$_3$F$_3$SAu: C, 58.39; H, 5.76; N, 4.01. Found: C, 60.18; H, 5.93; N, 4.29. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.56 (s, 36H, -CH$_3$), 2.06-2.19 (m, 6H, -CH$_2$-), 6.30 (s, 2H), 6.81 (s, 2H), 7.38-7.44 (m, 2H), 7.46-7.52 (m, 2H), 7.71-7.76 (m, 2H), 7.86-7.91 (m, 2H), 7.97 (t, 2H, $J$ = 7.74), 8.26 (s, 2H). $^{19}$F NMR (400 MHz, CDCl$_3$): δ -72.33. FAB-MS (+ve, m/z): 917 [M$^+$].

**Complex 5** Au(CNC)$_2$Cl (40.00 mg, 0.087 mmol), substituted imidazolium iodide (20.61 mg, 0.092 mmol) and KO'Bu (11.20 mg, 0.100 mmol) were refluxed in 25 mL CH$_3$CN overnight under an inert atmosphere. After 24 hours, a saturated LiOSO$_2$CF$_3$ solution in CH$_3$CN was added and the mixture was stirred at room temperature for another 30 minutes. The mixture was gravity filtered and the filtrate was collected. The filtrate was concentrated to about 5 mL, excess Et$_2$O was added and the mixture was kept $<$10 °C for 1 day. Pale yellow solid was formed. Yield: 49.32 mg, 82.6 %.

**Complex 6**: Synthesized and treated similar to that of complex 1. Yield: 93.1 mg, 69.4 %. Anal. Calcd for C$_{27}$H$_{32}$N$_3$O$_3$F$_2$S$_2$Au: C, 58.39; H, 5.76; N, 4.01. Found: C, 61.38; H, 6.27; N, 4.18. $^1$H NMR (400 MHz, CD$_3$CN): δ 3.85 (s, 6H, -CH$_3$), 7.02-7.07 (m, 2H), 7.17-7.23 (m, 7H), 7.31 (d, 4H, $J$ = 6.17), 8.37 (s, 2H). $^{19}$F NMR (400 MHz, CDCl$_3$): δ -79.33. FAB-MS (+ve, m/z): 606 [M$^+$].

**Complex 7**: Synthesized and treated similar to that of complex 2. An orange-brown solid was formed. Anal. Calcd for C$_{50}$H$_{52}$N$_6$O$_8$F$_6$S$_4$Au$_2$: C, 44.93; H, 3.32; N, 5.33. Found: C, 45.36; H, 3.59; N, 5.65. $^1$H NMR (300 MHz, CD$_2$Cl$_2$): δ 0.89-0.97 (m, 6H, $^-$Bu), 1.31-1.47 (m, 4H, $^-$Bu), 1.79-1.89 (m, 4H, $^-$Bu), 4.13-4.21 (m, 4H, $^-$Bu), 6.64-6.68 (m, 2H), 7.14-7.20 (m, 8H), 7.28-7.63 (m, 10H), 7.95-8.06 (m, 8H), 8.61 (s ,2H), 10.28 (s, 2H). FAB-MS (+ve, m/z): 1429 [M$^+$+ OSO$_2$CF$_3$], 1279 [M$^+$].
Complex 8: Synthesized and treated similar to that of complex 1, using methoxyphenyl-substituted extended Au(CNC)Cl (104.5 mg, 0.1566 mmol), \(N,N'\)-dimethylimidazolium iodide (36.9 mg, 0.1644 mmol) and KO\(^+\)Bu (20 mg, 0.1700 mmol). Yellow solid was formed. Yield: 106.8 mg, 77.6 %. Anal. Calcd for C\(_{38}\)H\(_{30}\)N\(_2\)O\(_4\)F\(_3\)S\(_2\)Au: C, 51.94; H, 3.44; N, 4.78. Found: C 53.27; H, 3.63; N, 4.89. \(^1\)H NMR (300 MHz, CD\(_2\)CN): \(\delta\) 3.81 (s, 3H, -OCH\(_3\)), 3.85 (s, 6H, -CH\(_3\) on carbene), 7.09-7.18 (m, 3H), 7.27-7.29 (m, 1H), 7.50-7.58 (m, 3H), 7.67-7.72 (m, 2H), 7.84-7.96 (m, 3H), 7.99-8.06 (m, 3H), 8.20 (t, 2H, \(J = 9.92\)), 8.49 (dd, 1H, \(J = 8.61\)), 8.54 (d, 1H, \(J = 7.73\)), 8.80 (s, 1H). \(^1\)F NMR (400 MHz, CDCl\(_3\)): \(\delta\) -79.31. FAB-MS (+ve, \(m/z\)): 728 [M\(^+\)].

Complex 9: Synthesized and treated similar to that of complex 2, using methoxyphenyl-substituted extended Au(CNC)Cl (123.0 mg, 0.1843 mmol), 1,1'-methylene bis(3-n-butylimidazolium) diiodide (47.6 mg, 0.0922 mmol) and KO\(^+\)Bu (22.4 mg, 0.2000 mmol). An intense yellow solid was formed. Yield: 147.2 mg, 43.7 %. Anal. Calcd for C\(_{58}\)H\(_{50}\)N\(_2\)O\(_4\)F\(_3\)S\(_2\)Au\(_2\): C, 53.29; H, 3.75; N, 4.60. Found: C, 55.08; H, 3.92; N, 4.72. \(^1\)H NMR (300 MHz, CD\(_2\)CN): \(\delta\) 0.47-0.52 (m, 6H, \(-^2\)Bu), 0.85-0.96 (m, 4H, \(-^2\)Bu), 1.79-1.85 (m, 4H, \(-^2\)Bu), 3.87 (s, 6H, -OCH\(_3\)), 3.99-3.96 (m, 4H, \(-^2\)Bu), 6.66-6.69 (m, 2H), 6.76-6.78 (m, 1H), 7.05-7.15 (m, 6H), 7.25-7.37 (m, 3H), 7.53-7.56 (m, 7H), 7.75-7.88 (m, 6H), 7.95-7.98 (m, 4H), 8.05-8.11 (m, 4H), 8.24 (s, 2H), 8.39-8.42 (1H), 8.52 (dd, 2H, \(J = 8.66\)), 8.84 (s, 2H). \(^1\)F NMR (400 MHz, CDCl\(_3\)): \(\delta\) -79.33. FAB-MS (+ve, \(m/z\)): 1674 [M\(^+\) + OSO\(_2\)CF\(_3\)], 1524 [M\(^+\)].

Complex 10: Synthesized and treated similar to that of complex 1, using methoxyphenyl-substituted extended Au(CNC)Cl (129.7 mg, 0.1958 mmol), \(N,N'\)-dimethylimidazolium iodide (48.0 mg, 0.2056 mmol) and KO\(^+\)Bu (26.0 mg, 0.2300 mmol). A pure brown solid was formed. Yield: 125.8 mg, 73.5 %. Anal. Calcd for C\(_{45}\)H\(_{37}\)N\(_2\)O\(_4\)F\(_3\)S\(_2\)Au: C, 46.74; H, 3.12; N, 6.41. Found: C, 48.07; H, 3.48; N, 6.58. \(^1\)H NMR (400 MHz, CD\(_2\)CN): \(\delta\) 3.84 (s, 6H, -CH\(_3\) on carbene), 3.87 (s, 3H, -OCH\(_3\)), 7.08-7.16 (m, 3H), 7.53-7.60 (m, 2H), 7.79 (t, 1H, \(J = 8.02\)), 7.94-7.98 (m, 2H), 8.06 (d, 2H, \(J = 7.90\)), 8.16 (s, 1H), 8.28 (d, 1H, \(J = 6.47\)), 8.31 (d, 1H, \(J = 8.18\)), 8.46 (d, 1H, \(J = 8.67\)), 8.79 (s, 1H), 9.12 (s, 1H). \(^1\)F NMR (400 MHz, CDCl\(_3\)): \(\delta\) -79.33. FAB-MS (+ve, \(m/z\)): 725 [M\(^+\)].

In general, the platinum(II)-based cyclometalated N-heterocyclic carbene complexes (Figure 2) can be synthesized by reaction of imidazolium salt of \(N,N'\)-dialkylimidazolium
halide (alkyl and halide = -CH₃ and I, (ligand 1); -CH₂CH₃ and I, (ligand 2); -CH₂CH₂CH₃ and Br, (ligand 3); -CH₂CH₂CH₂CH₃ and Br (ligand 4)) or 1,1'-alkylene bis(3-n-butylimidazolium) diiodide [0.5 equivalent; alkyl = methylene, (ligand 5); propylene, (ligand 6)] with equivalent amount of potassium tert-butoxide and appropriate type of precursor [Pt(CN)₃Cl] complexes under an inert atmosphere gave corresponding mononuclear and binuclear platinum(II) complexes.

Analytical data for the [PtII₃(CNN)₃(NHC)]++ complexes are shown below:

**Complex 11.** Yield: 70.1 mg, 84.0%. Anal. Calcd for C₂₁H₁₉N₄PF₆Pt: C, 37.78; H, 2.85; N, 8.40. Found: C, 38.01; H, 2.95; N, 8.29. ¹H NMR (400 MHz, CD₂CN): δ 3.82 (s, 6H, -CH₃), 6.47 (d, 1H, J = 7.90), 7.05 (t, 1H, J = 9.86), 7.11 (t, 1H, J = 9.15), 7.31 (m, 2H), 7.60 (m, 2H), 7.88 (d, 1H, J = 8.14), 8.00 (d, 1H, J = 8.01), 8.11 (t, 1H, J = 8.05), 8.23 (m, 3H). ¹³C NMR (126 MHz, CD₂CN): δ 39.03 (Me), 120.54, 123.82, 125.29, 125.92, 126.59, 129.59, 132.51, 137.72, 141.68, 142.57, 153.44 (carbene). ³¹P NMR (400 MHz, CD₃CN): δ -144.52. ¹⁹F NMR (400 MHz, CD₂CN): δ -73.12. FAB-MS (+ve, m/z): 522 [M⁺].

**Complex 12.** Yield: 40.1 mg, 85.1%. Anal. Calcd for C₂₃H₂₅N₄PF₆Pt: C, 39.71; H, 3.31; N, 8.06. Found: C, 38.77; H, 3.50; N, 7.82. ¹H NMR (400 MHz, CD₂CN): δ 1.35 (t, 6H, CH₃, J = 7.28), 4.28 (q, 4H, -CH₂-, J = 3.64), 6.44 (d, 1H, J = 7.01), 7.03 (t, 1H, J = 7.40), 7.12 (t, 1H, J = 7.55), 7.37 (m, 2H), 7.59 (m, 2H), 7.88 (d, 1H, J = 8.10), 7.99 (d, 1H, J = 7.96), 8.12 (t, 1H, J = 8.05), 8.22 (m, 3H). ¹³C NMR (126 MHz, CD₂CN): δ 15.87 (Et), 46.59 (Et), 120.45, 120.76, 125.32, 125.93, 126.51, 129.69, 132.51, 137.97, 141.71, 142.58, 153.27 (carbene). ³¹P NMR (400 MHz, CD₂CN): δ -144.52. ¹⁹F NMR (400 MHz, CD₂CN): δ -72.46. FAB-MS (+ve, m/z): 550 [M⁺].

**Complex 13.** Yield: 70.1 mg, 78.6 %. Anal. Calcd for C₂₅H₂₇N₄PF₆Pt: C, 41.49; H, 3.73; N, 7.75. Found: C, 42.36; H, 3.95; N, 8.07. ¹H NMR (400 MHz, CD₂CN): δ 0.74 (t, 6H, J = 7.39, -CH₃ on -¹Pr), 1.82 (sestet, 4H, J = 7.33, -CH₂- on -¹Pr), 4.24 (t, 4H, J = 7.11, -N-CH₂- on -¹Pr), 6.41 (d, 1H, J = 7.36), 6.95 (t, 1H, J = 7.38), 7.03 (t, 1H, J = 8.04), 7.50-7.52 (m, 2H), 7.61 (d, 1H, J = 7.59), 7.70 (t, 1H, J = 6.49), 8.00 (dd, 1H, J = 5.34), 8.15-8.19 (m, 2H), 8.32 (t, 1H, J = 7.88), 8.38 (d, 1H, J = 5.35), 8.47 (d, 1H, J = 8.03). ³¹P NMR (400 MHz, CD₂CN): δ -144.25. ¹⁹F NMR (400 MHz, CD₂CN): δ -73.66. FAB-MS (+ve, m/z): 578 [M⁺].
Complex 14. Yellow crystal available for single crystal X-ray diffraction was formed by slow diffusion of Et₂O into CH₂CN. Yield: 70.1 mg, 78.6%. Anal. Calcd for C₄ₓH₆ₓNa₅P₂F₁₂Pt₂: C, 43.14; H, 4.13; N, 7.46. Found: C, 42.86; H, 4.26; N, 7.51. ¹H NMR (400 MHz, CD₃CN): δ 0.75 (t, 6H, J = 7.36, -CH₃ on -Bu), 1.22 (sextet, 4H, J = 7.50, -CH₂- on -Bu), 1.79 (sextet, 4H, J = 7.53, -CH₂- on -Bu), 4.19-4.26 (m, 4H, -N-CH₂- on -Bu), 6.47 (d, 1H, J = 7.43), 7.03 (t, 1H, J = 6.78), 7.12 (t, 1H, J = 7.52), 7.32-7.36 (m, 2H), 7.60 (d, 2H, J = 6.74), 7.88 (d, 1H, J = 8.09), 7.99 (d, 1H, J = 7.90), 8.12 (t, 1H, J = 8.06), 8.23 (m, 3H). ³¹P NMR (400 MHz, CD₃CN): δ -144.52. ¹⁹F NMR (400 MHz, CD₃CN): δ -73.86. FAB-MS (+ve, m/z): 606 [M⁺].

Complex 15. Orange crystal available for single crystal X-ray diffraction was formed by slow diffusion of Et₂O into CH₂CN. Yield: 37.2 mg, 82.0%. Anal. Calcd for C₄ₓH₄ₓNa₅P₂F₁₂Pt₂: C, 40.23; H, 3.28; N, 7.99. Found: C, 41.06; H, 3.41; N, 8.18. ¹H NMR (400 MHz, CD₃CN): δ 0.58-0.64 (m, 6H, -Bu), 0.99-1.12 (m, 4H, -Bu), 1.63-1.78 (m, 4H, -Bu), 3.93-4.19 (m, 4H, -Bu), 6.21 (d, 1H, J = 7.05), 6.29 (d, 1H, J = 7.56), 6.33 (d, 1H, J = 7.56), 6.65 (t, 1H, J = 7.42), 6.71 (t, 1H, J = 7.41), 6.84-6.88 (m, 3H), 7.11-7.16 (m, 3H), 7.22 (d, 1H, J = 7.42), 7.41-7.45 (m, 3H), 7.55 (d, 1H, J = 7.43), 7.55-7.61 (m, 2H), 7.80-7.87 (m, 6H), 7.95-8.00 (m, 4H). ¹³C NMR (126 MHz, CD₃CN): δ 13.64 (-Bu), 19.86 (-Bu), 33.12 (-Bu), 51.40 (-Bu), 120.36, 120.59, 120.98, 122.59, 122.77, 124.07, 124.37, 125.42, 125.73, 126.71, 129.07, 129.34, 131.97, 132.18, 136.96, 141.41, 152.35 (carbene), 162.28 (carbene). ³¹P NMR (400 MHz, CD₃CN): δ -144.51. ¹⁹F NMR (400 MHz, CD₃CN): δ -72.87. FAB-MS (+ve, m/z): 1257 [M⁺ + PF₆⁻], 1112 [M⁺].

Complex 16. Yield: 37.2 mg, 82.0%. Anal. Calcd for C₄ₓH₅ₓNa₅P₂F₁₂Pt₂: C, 41.12; H, 3.50; N, 7.83. Found: C, 41.06; H, 3.41; N, 8.08. ¹H NMR (400 MHz, CD₃CN): δ 0.62-0.70 (m, 3H), 0.75 (t, 3H, J = 7.33), 0.86 (t, 2H, J = 7.33), 0.92-0.99 (m, 2H), 1.04-1.14 (m, 2H), 1.17-1.24 (m, 2H), 1.56-1.70 (m, 2H), 1.76-1.85 (m, 2H), 2.33-2.50 (m, 2H), 3.98-4.13 (m, 2H), 6.26-6.31 (m, 1H), 6.49 (t, 1H, J = 7.52), 6.81 (t, 1H, J = 6.89), 6.85 (t, 1H, J = 7.45), 6.92 (t, 1H, J = 7.65), 6.99-7.09 (m, 2H), 7.12-7.18 (m, 2H), 7.20 (t, 1H, J = 8.17), 7.35-7.49 (m, 5H), 7.58-7.63 (m, 2H), 7.71 (d, 1H, J = 8.07), 7.80-7.85 (m, 1H), 7.90-7.93 (m, 1H), 7.99-8.07 (m, 2H), 8.09-8.17 (m, 2H), 8.17-8.24 (m, 2H). ¹³C NMR (126 MHz, CD₃CN): δ 13.76, 20.14, 23.81, 33.12, 51.40, 51.78, 120.43, 120.73, 122.38, 122.84, 124.47, 125.27, 125.97, 126.44, 129.55, 129.96, 131.21, 132.46, 137.93, 142.77, 162.47 (carbene), 165.18 (carbene). ³¹P NMR (400 MHz, CD₃CN): δ -144.53. ¹⁹F NMR (400 MHz, CD₃CN): δ -72.90. FAB-MS (+ve, m/z): 1285 [M⁺ + PF₆⁻], 1140 [M⁺].
Complex 17. Yield: 75.9 mg, 94.0 %. Anal. Calcd for C_{31}H_{32}N_{4}PF_{6}Pt: C, 46.50; H, 4.03; N, 7.00. Found: C, 46.86; H, 4.28; N, 7.32. $^{1}$H NMR (400 MHz, CD$_3$CN): δ 0.81 (t, 6H, J = 6.15, -CH$_3$ on $^{2}$Pr), 1.80-1.89 (m, 4H, -CH$_2$- on $^{2}$Pr), 4.19-4.25 (m, 4H, -CH$_2$-N on $^{2}$Pr), 6.51 (d, 1H, J = 7.40), 7.05 (t, 1H, J = 7.38), 7.14 (t, 1H, J = 7.24), 7.34-7.38 (m, 2H), 7.58-7.66 (m, 4H), 7.74 (d, 1H, J = 6.55), 7.94-7.98 (m, 2H), 8.13 (s, 1H), 8.23-8.28 (m, 3H), 8.41 (d, 1H, J = 7.98). $^{13}$C NMR (126 MHz, CD$_3$CN): δ 11.28 ($^{2}$Pr), 24.64 ($^{2}$Pr), 53.34 ($^{2}$Pr), 122.71, 125.45, 125.84, 126.63, 128.62, 130.37, 131.58, 132.49, 137.94, 141.61, 153.20, 154.82, 155.77, 165.33 (carbene). $^{31}$P NMR (400 MHz, CD$_3$CN): δ -144.54. $^{19}$F NMR (400 MHz, CD$_3$CN): δ -73.79. FAB-MS (+ve, m/z): 807 [M$^+$].

Complex 18. Yield: 54.1 mg, 90.3 %. Anal. Calcd for C$_{39}$H$_{48}$N$_{4}$PF$_{6}$Pt: C, 51.31; H, 5.30; N, 6.14. Found: C, 52.63; H, 5.51; N, 6.35. $^{1}$H NMR (400 MHz, CD$_3$CN): δ 0.82 (t, 6H, J = 7.38, $^{2}$Pr), 1.44 (s, 18H, $^{2}$Bu), 1.80-1.86 (m, 4H, $^{2}$Pr), 4.16-4.25 (m, 4H, $^{2}$Pr), 6.09 (t, 2H, J = 6.31), 6.51 (d, 1H, J = 7.39), 7.05 (t, 1H, J = 7.41), 7.15 (t, 1H, J = 7.55), 7.35-7.38 (m, 2H), 7.58-7.63 (m, 1H), 7.70-7.73 (m, 2H), 7.79 (d, 1H, J = 7.69), 8.10 (s, 1H), 8.22-8.26 (m, 2H), 8.46 (d, 1H, J = 7.99). $^{13}$C NMR (126 MHz, CDCl$_3$): δ 10.77 ($^{2}$Pr), 24.65 ($^{2}$Pr), 31.65 ($^{2}$Bu), 53.38 ($^{2}$Pr), 122.71, 123.11, 125.78, 126.77, 129.62, 132.43, 137.81, 149.67, 141.52, 148.89, 153.26, 155.57, 159.25, 165.16 (carbene). $^{31}$P NMR (400 MHz, CD$_3$CN): δ -144.73. $^{19}$F NMR (400 MHz, CD$_3$CN): δ -72.93. FAB-MS (+ve, m/z): 768 [M$^+$].

Complex 19. Yield: 81.9 mg, 41.4 %. Anal. Calcd for C$_{59}$H$_{66}$N$_{2}$P$_{2}$F$_{12}$Pt$_{2}$: C, 45.51; H, 3.62; N, 7.20. Found: C, 45.82; H, 3.72; N, 7.26. $^{1}$H NMR (400 MHz, CD$_3$CN): δ 0.58-0.64 (m, 6H, $^{2}$Bu), 0.98-1.38 (m, 8H, $^{2}$Bu), 3.89-4.06 (m, 4H, $^{2}$Bu), 6.20-6.49 (m, 3H), 6.67-6.75 (m, 2H), 6.89-6.93 (m, 2H), 7.12-7.16 (m, 2H), 7.31 (d, 1H, J = 7.61), 7.39-7.46 (m, 6H), 7.50-7.54 (m, 2H), 7.59-7.67 (m, 4H), 7.71-7.76 (m, 4H), 7.83-7.88 (m, 4H), 7.98-8.04 (m, 4H), 8.18 and 8.31 (m, 2H). $^{13}$C NMR (126 MHz, CD$_3$CN): δ 13.63 ($^{2}$Bu), 19.86 ($^{2}$Bu), 33.01 ($^{2}$Bu), 51.29 ($^{2}$Bu), 125.67, 126.91, 128.41, 131.72, 131.98, 136.87, 141.27, 145.21, 152.29, 154.46, 155.52, 156.24, 165.45 (carbene). $^{31}$P NMR (400 MHz, CD$_3$CN): δ -144.69. $^{19}$F NMR (400 MHz, CD$_3$CN): δ -72.97. FAB-MS (+ve, m/z): 1413 [M$^+$ + PF$_6$], 1268 [M$^+$].

Complex 20. Yield: 56.6 mg, 52.5 %. Anal. Calcd for C$_{75}$H$_{86}$N$_{6}$P$_{2}$F$_{12}$Pt$_{2}$: C, 50.56; H, 4.98; N, 6.29. Found: C, 57.21; H, 5.09; N, 6.43. $^{1}$H NMR (400 MHz, CD$_3$CN): δ 0.79-0.83 (m, 6H, $^{2}$Bu), 1.10-1.22 (m, 4H, $^{2}$Bu), 1.45 (s, 36H, $^{2}$Bu), 3.52-3.72 (m, 4H, $^{2}$Bu), 5.93-5.96 (m, 2H), 6.24-6.30 and 6.43-6.48 (m, 2H), 6.85-6.96 (m, 2H), 7.10-7.19 (m, 2H), 7.27-7.51 (m, 4H), 7.53-7.62 (m, 4H), 7.89-7.91 (m, 1H), 8.04-8.06 (m, 1H), 8.14-8.19 (m, 2H), 8.35-8.41 (m, 2H), 8.51 (d, 1H, J = 8.81), 8.69-8.71 and 8.76-8.79 (m, 2H). $^{13}$C NMR (126 MHz, CD$_3$CN): δ 13.61 ($^{2}$Bu), 19.82 ($^{2}$Bu), 31.68 ($^{2}$Bu), 33.03 ($^{2}$Bu), 51.32 ($^{2}$Bu), 126.73, 127.61, 129.41, 130.72, 131.98, 134.31, 140.69, 143.34, 151.07, 153.85, 154.97,
155.63, 165.35 (carbene). $^{31}$P NMR (400 MHz, CD$_3$CN): $\delta$ -144.75. $^{19}$F NMR (400 MHz, CD$_3$CN): $\delta$ -73.07. FAB-MS (+ve, m/z): 1637 [M$^+$ + PF$_6$], 1492 [M$^+$].

**Complex 21.** Yield: 113.7 mg, 75.9 %. Anal. Calcd for C$_{36}$H$_{39}$N$_4$PF$_6$Pt: C, 49.83; H, 4.53; N, 6.46. Found: C, 50.07; H, 4.72; N, 6.51. $^1$H NMR (400 MHz, CD$_3$CN): $\delta$ 0.79 (t, 6H, J = 7.36, $^6$Pr), 1.71-1.91 (m, 4H, $^3$Pr), 4.31 (t, 4H, J = 7.23, $^6$Pr), 6.89 (s, 1H), 7.33-7.47 (m, 4H), 7.52-7.65 (m, 1H), 7.83-7.89 (m, 2H), 8.01 (t, 1H, $J$ = 7.58), 8.21-8.19 (m, 2H), 8.19 (d, 1H, $J$ = 6.32), 9.01-9.05 (m, 1H). $^{13}$C NMR (126 MHz, CD$_3$CN): $\delta$ 11.29 ($^6$Pr), 24.57 ($^6$Pr), 53.44 ($^6$Pr), 120.51, 120.92, 122.84, 123.93, 126.25, 127.72, 129.19, 129.77, 129.98, 131.14, 131.90, 132.35, 134.76, 135.23, 136.05, 136.57, 141.51, 147.92, 151.74, 162.56 (carbene). $^{31}$P NMR (400 MHz, CD$_3$CN): $\delta$ -145.13. $^{19}$F NMR (400 MHz, CD$_3$CN): $\delta$ -73.16. FAB-MS (+ve, m/z): 680 [M$^+$].

**Complex 22.** Yellow crystal available for single crystal X-ray diffraction is formed via recrystallization from CH$_3$CN/Et$_2$O. Yield: 56.6 mg, 52.5 %. Anal. Calcd for C$_{66}$H$_{64}$N$_2$P$_2$F$_2$Pt$_2$: C, 48.06; H, 3.91; N, 6.79. Found: C, 48.32; H, 4.06; N, 6.85. $^1$H and $^{13}$C NMR: not available due to moderate solubility in common deuterated NMR solvents. FAB-MS (+ve, m/z): 1315 [M$^+$].

**Complex 23.** A mixture of [Pt(CN)$_2$Cl] (45 mg, 0.098 mmol), 1-(3-hydroxy-propyl)-3-(2,4,6-trimethyl-phenyl)-imidazolium bromide (33 mg, 0.1 mmol) and KO'Bu (14 mg, 0.12 mmol) were dissolved in CH$_3$CN (15 mL) and refluxed overnight. A dark yellow solution was formed. A saturated NH$_4$PF$_6$ solution in CH$_3$CN was added and stirred at 50°C for 1 hour. The reaction mixture was treated similar to that of complex 11, orange solid was washed by Et$_2$O and dried under vacumm. Yield: 95 g (86.2 %). $^1$H NMR (400 MHz, CD$_3$CN): $\delta$ = 2.05 (s, 1H, -OH), 2.07 (s, 6H, -CH$_3$), 2.35 (s, 3H, -CH$_3$), 3.51-3.56 (m, 2H, -propylene-), 4.34-4.43 (m, 2H, -propylene-), 4.52-4.57 (m, 2H, -propylene-), 6.70 (d, 1H, $J$ = 7.3 Hz), 6.85 (s, 2H), 7.04-7.12 (m, 2H), 7.30 (s, 1H), 7.52 (d, 1H, $J$ = 7.5 Hz), 7.58-7.64 (m, 2H), 7.80 (d, 1H, $J$ = 8.1 Hz), 7.90 (d, 1H, $J$ = 8.0 Hz), 8.05 (t, 1H, $J$ = 8.1 Hz), 8.15-8.20 (m, 2H), 8.32 (d, 1H, $J$ = 5.3 Hz). $^{13}$C NMR (500 MHz, CD$_3$CN): $\delta$ = 20.89, 34.02, 49.67, 59.36, 120.76, 123.16, 125.24, 125.45, 126.98, 126.36, 129.15, 129.67, 130.23, 132.07, 138.72, 142.53, 155.32, 165.32. FAB-MS (+ve, m/z): 671 [M$^+$]. elemental analysis calcd (%) for C$_{33}$H$_{31}$N$_4$OPF$_6$Pt: C, 45.65; H, 3.83; N, 6.87; found: C, 45.76 H, 3.85; N, 6.98.

**Complex 24.** A mixture of extended [Pt(CN)$_2$Cl] (85 mg, 0.17 mmol), N,N'-di-n-propylimidazolium bromide (41 mg, 0.18 mmol) and KO'Bu (21 mg, 0.19 mmol) were dissolved in CH$_3$CN (15 mL) and refluxed overnight. A clear yellow solution was
formed. A saturated NH₄PF₆ solution in CH₂CN was added and stirred at 50°C for 1 hour. The reaction mixture was cooled to room temperature, yellow solid was formed and collected via filtration, the solid was washed by Et₂O and dried under vacumm. Yield: 0.34 g (80.0 %).

¹H NMR (400 MHz, CD₃CN): δ = 0.81 (t, 6H, J = 7.4 Hz, -²Pr), 1.72-1.87 (m, 4H, -²Pr), 4.25 (t, 4H, J = 7.2 Hz), 6.50 (d, 1H, J = 7.3 Hz), 7.05 (t, 1H, J = 7.0 Hz), 7.14 (t, 1H, J = 7.5 Hz), 7.38-7.41 (m, 2H), 7.64 (d, 1H, J = 7.0 Hz), 7.76-7.92 (m, 2H), 8.00-8.19 (m, 5H), 8.75 (s, 1H), 8.95 (s, 1H). ¹³C NMR (500 MHz, CD₃CN): δ = 11.27 (-²Pr), 24.61 (-²Pr), 53.25 (-²Pr), 120.19, 122.75, 123.89, 125.72, 126.22, 129.08, 129.99, 131.89, 132.24, 132.64, 137.78, 142.23, 156.89, 164.65. FAB-MS (+ve, m/z): 629 [M⁺]. elemental analysis calcd (%) for C₂₉H₂₅N₄PF₆Pt: C, 45.02; H, 3.78; N, 7.24; found: C, 45.12; H, 3.97; N, 7.39.

**Complex 25.** A mixture of extended [Pt(CNN)Cl] (70 mg, 0.14 mmol), N-n-butyl-N’-(2-hydroxyethyl)imidazolium bromide (36 mg, 0.15 mmol) and KO'Bu (19 mg, 0.16 mmol) were dissolved in CH₂CN (15 mL) and refluxed overnight. An clear orange solution was formed. A saturated NH₄PF₆ solution in CH₂CN was added and stirred at 50°C for 1 hour. The reaction mixture was cooled to room temperature, the solvent was evaporated to give rise a yellow solid. The crude product was dissolved in CHCl₃. the insoluble impurities were filtered and discarded. The clear yellow filtrate was concentrated to 5 mL, excess Et₂O was added. The solution was stored < 10 °C overnight. Yellow crystalline solid was formed and collected via filtration, the solid was washed by Et₂O and dried under vacuum. Yield: 95 g (86.2 %).

¹H NMR (400 MHz, CD₃CN): δ = 0.72 (t, 3H, J = 7.4 Hz, -²Bu), 1.20-1.29 (m, 2H, -²Bu), 1.78-1.87 (m, 2H, -²Bu), 1.98 (s, 1H, -OH), 3.77-3.86 (m, 2H, -²Bu), 4.25-4.32 (m, 2H, -ethylene-), 4.46-4.52 (m, 2H, -ethylene-), 6.49 (d, 1H, J = 7.4 Hz), 7.05 (t, 1H, J = 7.4 Hz), 7.14 (t, 1H, J = 7.5 Hz), 7.39 (s, 1H), 7.45 (s, 1H), 7.63 (d, 1H, J = 7.7 Hz), 7.83-7.89 (m, 2H), 8.02 (t, 1H, J = 7.6 Hz), 8.09 (d, 1H, J = 8.0 Hz), 8.13-8.18 (m, 3H), 8.75 (s, 1H), 9.03 (s, 1H). ¹³C NMR (500 MHz, CD₃CN): δ = 13.76 (-²Bu), 20.23 (-²Bu), 33.18 (-²Bu), 51.48 (-²Bu), 54.12, 61.66, 120.12, 122.60, 123.35, 123.79, 125.72, 126.22, 129.09, 130.00, 131.88, 132.27, 135.26, 136.61, 137.73, 142.32, 148.78, 151.74, 157.38, 164.65. FAB-MS (+ve, m/z): 645 [M⁺]. elemental analysis calcd (%) for C₂₉H₂₉N₄OPF₆Pt: C, 44.11; H, 3.70; N, 7.10; found: C, 44.36; H, 3.81; N, 7.15.
Example 2: In vitro cytotoxicity of the cyclometalated N-heterocyclic carbene complexes

Example 2 describes the in vitro cytotoxicity, which is indicative of the induction of cell death and/or inhibition of cellular proliferation of cancer cells, of the cyclometalated N-heterocyclic complexes on cervical epithelioid carcinoma, hepatocellular carcinoma, leukemia, nasopharyngeal carcinoma, breast carcinoma, melanoma, and lung carcinoma.

By means of MTT assays, the cytotoxic properties of cyclometalated N-heterocyclic carbene complexes (1–25) were determined toward some established human cancer cell lines including hepatocellular carcinoma (HepG2), cervical epithelioid carcinoma (HeLa), epithelial carcinoma (KB and its camptothecin-resistant cell line KB100), non-small cell lung carcinoma (NCI-H460), leukemia (HL-60), breast carcinoma (MDA-MB-231), melanoma (B16) and nasopharyngeal carcinoma (SUNE1). The IC\textsubscript{50} values (dose required to inhibit 50% cellular growth for 72 h) of the gold(III) complexes are listed in Table 1. All the [Au\textsuperscript{III}(CNC)\textsubscript{n}(NHC)]\textsuperscript{m+} complexes exhibit promising cytotoxicity toward these cell lines with IC\textsubscript{50} values span over the range of 0.15 to 28 \(\mu\text{M}\). In terms of the IC\textsubscript{50} values, they display similar cytotoxic properties compared to the reference complexes cisplatin and camptothecin (CPT). Among them, complex 1 exhibits the highest cytotoxic activity toward all the cancer cell lines (except KB) and displays a \(~18\) to 28 fold higher cytotoxic activity than cisplatin.

Using lung fibroblast cells (CCD-19Lu), the cytotoxicity of the complexes to non-cancerous cells was also examined. As shown in Table 1, the examined complexes examined in general have higher cancer-cell specificity and results in more cytotoxic to cancer cell than the fibroblast cells.

| Table 1. The IC\textsubscript{50} values (\(\mu\text{M}, 72\text{ h}\)) of [Au\textsuperscript{III}(CNC)\textsubscript{n}(NHC)]\textsuperscript{m+} complexes against selected human cancer cell lines. |
|---------------|---------|-------|-------|-------|-------|-------|-------|-------|
|               | HepG2   | HeLa  | KB    | KB100 | SUNE1 | NCI   | MBA-MD | B16   | HL-60 | CCD-H460 | CCD-231 | 19Lu |
| IC\textsubscript{50} (\(\mu\text{M}\)) | 0.37    | 0.15  | 0.56  | 1.2   | 0.25  | 0.17  | 0.62   | 0.33  | 0.48  | 25       |         |      |
| 1             | 7.9     | 7.8   | 10    | 28    | 3.3   | 3.0   | 4.2    | 10    | 5.9   | >100    |         |      |
| 2             |         |       |       |       |       |       |        |       |       |         |         |      |
|   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18  | 19  | 20  | 21  | 22  | 23  | 24  | 25  | cisplatin |
|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|   | 1.1 | 2.4 | 2.3 | 12  | 3.0 | 1.2 | 1.7 | 2.2 | 2.6 | 16  |    |    |    |    |    |    |    |    |    |    |    |    | 14.6 |
|   | 1.9 | 2.7 | 3.6 | 4.5 | 5.5 | 6.2 | 3.7 | 7.7 | 1.1 | 11  |    |    |    |    |    |    |    |    |    |    |    |    | 14.9 |
|   | 2.6 | 3.5 | 4.4 | 4.0 | 3.4 | 9.5 | 13  | 2.1 | 1.2 | 11  |    |    |    |    |    |    |    |    |    |    |    |    | 2.4 |
|   | 18  | 3.9 | 20  | 9.4 | 0.7 | 11  | 8.5 | 3.3 | 7.1 | 48  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 20  | 5.6 | 15  | 6.7 | 0.9 | 12  | 8.4 | 11  | 8.2 | 20  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 1.0 | 0.5 | 0.42 | 18  | 0.26 | 0.18 | 0.96 | 0.56 | 0.13 | 0.89 |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 4.5 | 7.2 | 5.0 | 3.8 | 4.5 | 5.5 | 6.2 | 9.1 | 7.1 | 9.9  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 2.5 | 1.1 | 1.3 | 9.5 | 4.2 | 9.6 | 3.3 | 3.4 | 7.1 | 6.5  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.31 | 0.33 | 0.66 | 0.62 | 0.51 | 0.58 | 1.5 | 3.1 | 0.58 | 5.7  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 1.3 | 0.48 | 0.89 | 0.77 | 0.32 | 0.57 | 1.2 | 1.8 | 0.52 | 2.1  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 1.1 | 0.05 | 0.14 | 0.13 | 0.16 | 0.18 | 0.28 | 0.42 | 0.56 | 12   |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.77 | 0.05 | 0.04 | 0.08 | 0.14 | 0.09 | 0.04 | 0.15 | 0.08 | 10   |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.49 | 0.55 | n.d. | n.d. | 0.86 | n.d. | n.d. | n.d. | n.d. | 10   |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.27 | 0.62 | n.d. | n.d. | 0.22 | n.d. | n.d. | n.d. | n.d. | 4.2  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.18 | 0.25 | n.d. | n.d. | 0.53 | n.d. | n.d. | n.d. | n.d. | 6.1  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.11 | 0.46 | n.d. | n.d. | 0.37 | n.d. | n.d. | n.d. | n.d. | 1.2  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.34 | 0.89 | n.d. | n.d. | 1.2  | n.d. | n.d. | n.d. | n.d. | 3.5  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.78 | 0.48 | n.d. | n.d. | 0.94 | n.d. | n.d. | n.d. | n.d. | 7.5  |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.88 | 0.55 | n.d. | n.d. | 0.71 | n.d. | n.d. | n.d. | n.d. | 12   |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |
|   | 0.68 | 0.45 | n.d. | n.d. | 0.88 | n.d. | n.d. | n.d. | n.d. | 11   |    |    |    |    |    |    |    |    |    |    |    |    | n.d. |

n.d. = not determined
Example 3: In vivo anti-cancer property of the cyclometalated N-heterocyclic carbene complexes

Example 3 describes the results of in vivo cytotoxicity study of complex 1 and complex 14.

Prompted by the prominent in vitro cytotoxicity and the potential cancer-cell selectivity, the in vivo anti-cancer property of complex 1 was preliminarily examined by using nude mice models with the approval from the Committee on the Use of Live Animals for Teaching and Research (The University of Hong Kong). As shown in Fig. 3, treatment of nude mice bearing PLC tumor (hepatocellular carcinoma) by complex 1 at 3 mg/kg/week for 28 days significantly suppressed (47%) tumor growth compared to that of the vehicle control. Importantly, no apparent 1-induced toxic side-effect including death and weight loss was observed during the whole course of the examination.

For the complex 14, four-week-old male BALB/c AnN-nu mice (nude mice) were obtained from the laboratory of PearL Materia Medica Development (Shenzhen) Ltd. Tumor cells (1 x 10⁶) resuspended in DMEM medium were implanted by subcutaneous injection on the right flank of the mice. When tumors were approximately 50 mm³ in size, animals were randomly separated into four groups to receive treatment of twice-a-week intraperitoneal injection of 20% PET vehicle control (20% PET = 12% polyethylene glycol 400; 6% ethanol; 2% Tween 20; 80% phosphate-buffered saline), complex 14 at 1 mg/kg, complex 14 at 3 mg/kg or cyclophosphamide at 30 mg/kg. Volumes of the tumor were measured every 3 to 4 days. Tumor volume was calculated by the formula: abc/2 in which a represents tumor length; b, the width; and c, tumor thickness, as measured with a caliper and expressed in millimeter. After 28 days, the mice were sacrificed and the tumors were taken out and their weights were measured.

Results demonstrated that injection of 3 mg/kg of complex 14 significantly inhibited the NCI-H460 tumor growth by 55%, whereas 1 mg/kg was significantly less effective (Fig. 3). Regular body-weight measurement showed that mice receiving either 3 or 1 mg/kg of complex 14 had no significant weight loss.

With respect to any figure or numerical range for a given characteristic, a figure or a parameter from one range may be combined with another figure or a parameter from a different range for the same characteristic to generate a numerical range.

Other than in the operating examples, or where otherwise indicated, all numbers,
values and/or expressions referring to quantities of ingredients, reaction conditions, etc.,
used in the specification and claims are to be understood as modified in all instances by the
term "about."

While the invention has been explained in relation to certain embodiments, it is to be
understood that various modifications thereof will become apparent to those skilled in the
art upon reading the specification. Therefore, it is to be understood that the invention
disclosed herein is intended to cover such modifications as fall within the scope of the
appendixed claims.

Example 4: Induction of apoptosis by the cyclometalated N-heterocyclic carbene
complexes

Example 4 describes the result of studies showing that complex 1 and complex 14
would induce apoptosis in SUNE1 cancer cells.

Since cancer is characterized by uncontrolled cellular proliferation, there is a
considerable interest in chemotherapeutic-induced apoptosis [J. C. Reed, Nature Rev. Drug
annexin V (AV-FITC) and propidium iodide (PI), the apoptosis-inducing properties of
complex 1 in SUNE1 cells were examined by flow cytometry. Upon treatment with
complex 1 (60 µM) for 72 h, 30.9% of SUNE1 cells were found to be in early apoptotic state.
The apoptosis-inducing properties of complex 1 at a lower dose (12 µM for 72 h) were also
examined. We found that ~90% of viable cells were unstained by both the AV-FITC and PI.
The percentage of cell death in cells treated with 1 at 12 µM (IC_{50} value) did not kill 50% of
cells. According to the propagation profiles (formazan absorbance A_{550nm} vs incubation time)
of the treated SUNE1 cells, there is a trend of cellular growth inhibition in the presence of
complex 1 at 12 µM level. Taken together with the flow cytometric results, complex 1
appears to inhibit cancer cell proliferation at 12 µM and induce apoptosis at higher doses (i.e.
60 µM).

The apoptosis-inducing properties of complex 14 in SUNE1 cells were also examined
by flow cytometry. Upon treatment with complex 14 (10 µM) for 72 h, 46.4% of SUNE1
cells were found to be in early apoptotic state. The apoptosis-inducing properties of
complex 14 at a lower dose (1 µM for 72 h) were also examined. We found that ~90% of
viable cells were unstained by both the AV-FITC and PI. Thus, complex 14 could induce
apoptosis at 10 µM.
Example 5: Inhibition or poisoning of topoisomerase by the gold(III) complexes

Example 5 describes the study of the topoisomerase poisoning and inhibition by complex 1.

DNA strand breaks were also detected in complex 1-treated KB cells by alkaline comet assay. The comet assay revealed that treatment with complex 1 (0.5 μM), CPT (1 μM) and a known DNA damaging agent doxorubicin (1 μg/ml) for 3 h induced extensive strand breaks on chromosomal DNA (Fig. 4). DNA cleavage events induced by CPT and complex 1, but not Dox, were partially reversed upon a second incubation at 55 °C for 10 min, suggesting that complex 1 and CPT could stabilize topoisomerase-cleavable complexes in cells. Topoisomerases have become one of the important cellular targets for anti-cancer treatment. It is believed that topoisomerase inhibitors prevent the ligation step of the cell cycle, generate DNA strand breaks, and subsequently induce apoptosis in cells. We recently have demonstrated that several platinum-based lipophilic cations and DNA intercalators such as [PtIII(C≡N≡N)]+ which exhibit prominent inhibitory activity on topoisomerase 1. To study the impact of complex 1 on the catalytic activity of TopoI, the TopoI-mediated relaxation of supercoiled DNA was measured. Complex 1 dose-dependently inhibits DNA relaxation at significant lower concentrations than CPT (Fig. 4, upper). Higher concentration (10 μM) completely inhibited the process. The assay was repeated on ethidium bromide containing gel (Fig. 4, lower). Under the same experimental condition, the presence of nicked DNA was observed, indicating that complex 1 may stimulate DNA cleavage by TopoI.

The band depletion assay has been used to demonstrate the formation of TopoI cleavable complexes. In this assay, while TopoI-DNA cleavable complexes are trapped by alkaline lysis, free TopoI is detected as an immunoreactive band. In KB cells, both complex 1 (10 and 100 nM) and CPT (1 μM) reduced the band intensity of the TopoI band with about equal efficiency.

To gain further insight into the structural basis of the TopoI-linked DNA complex stabilization by complex 1, we used flexible-ligand docking module of ICM-Pro 3.6-1 molecular software (Molsoft). Analysis of the low energy metal complex conformations suggested that complex 1 binds to TopoI-linked DNA in a similar manner to topotecan (Fig. 5), with a strong binding interaction (as reflected by the score of –34.57). The top-scoring binding pose of 1 is characterized by the C≡N≡C motif being in close contact with amino acid residue G12, C112, K532, N722 and the carbene group of complex 1 pointing towards N352.
Claims

What is claimed is:

1. Use of a cyclometalated N-heterocyclic carbene complex having one of the following formulae (I to IV) in manufacturing a medicament for treating cancer:

```
[ R^{1} ]^{n}  [ R^{8} ]^{n}
R^{2}  R^{3} \quad R^{9}  R^{10}
R^{11}  R^{12}
```

```
[ R^{13} ]^{n}  [ R^{18} ]^{n}
R^{14}  R^{16} \quad R^{19}  R^{21}
R^{20}  R^{22}
```

```
[ R^{26} ]^{n}  [ R^{29} ]^{n}
R^{27}  R^{28} \quad R^{30}  R^{31}
R^{32}  R^{34}
```

\text{or a pharmaceutically acceptable salt thereof, wherein,}

- \( M \) is selected from the metal ion of \( \text{Au}^{3+} \) or \( \text{Pt}^{2+} \);

- \( X \) is selected from a carbon atom or a nitrogen atom;
- R₁, R₈, R₁³, R₁⁸, R₂⁶, and R₂⁹ are each independently selected from the group consisting of -H, 

- R₂, R₃, R₄, R₅, R₉, R₁⁰, R₁⁴, R₁⁵, R₁₆, R₁₇, R₁⁹, R₂₀, R₂¹, R₂₂, R₂⁷, R₂⁸, R₃¹, and R₃² are each independently selected from the group consisting of -H and -NO₂; or each pair of R₂ and R₃, R₄ and R₅, R₉ and R₁⁰, R₁⁴ and R₁⁵, R₁₆ and R₁₇, R₁⁹ and R₂₀, R₂¹ and R₂², R₂⁷ and R₂⁸, R₃¹ and R₃² is independently joined together to form 

- R₆, R₇, R₁₁, R₁², R₂³, R₂⁴, R₃² and R₃³ are each independently selected from the group consisting of -CH₃, -C₂H₅, -C₃H₇, -C₄H₉, -CH₂OH, -C₂H₄OH, -C₃H₆OH, 

- R₂⁵ and R₃⁴ are each independently selected from the group consisting of -CH₂-, -C₂H₄-, -C₃H₆- and -C₄H₈-;

- Each A is independently a pharmaceutically acceptable counter-ion;

- n is an integer ranging from 0 to +4;

- b is an integer ranging from -4 to -1;

- y is equal to the absolute value of n/b when n is >0; and

- yAᵇ is absence when n is equal to 0.

2. The use of claim 1, wherein the complex has formulae I, and wherein,
- M is Au³⁺;
- X is a carbon atom;
- R¹, R², R³, R⁴, and R⁵ are each -H;
- \( R^6 \) and \( R^7 \) are each \(-\text{CH}_3\);
- \( A \) is a \( \text{OSO}_2\text{CF}_3 \) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex I).

3. The use of claim 1, wherein the complex has formulae III, and wherein,
   - \( M \) is \( \text{Au}^{3+} \);
   - \( X \) is a carbon atom;
   - \( R^{13} \) and \( R^{18} \) are each \(-\text{H}\);
   - \( R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21} \) and \( R^{22} \) are each \(-\text{H}\);
   - \( R^{23} \) and \( R^{24} \) are each \(-\text{C}_4\text{H}_9\);
   - \( R^{25} \) is \(-\text{CH}_2\text{-}\);
   - \( A \) is a \( \text{OSO}_2\text{CF}_3 \) anion;
   - \( n \) is +2;
   - \( b \) is -1; and
   - \( y \) is 2 (complex 2).

4. The use of claim 1, wherein the complex has formulae III, and wherein,
   - \( M \) is \( \text{Au}^{3+} \);
   - \( X \) is a carbon atom;
   - \( R^{13} \) and \( R^{18} \) are each \(-\text{H}\);
   - \( R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21} \) and \( R^{22} \) are each \(-\text{H}\);
   - \( R^{23} \) and \( R^{24} \) are each \(-\text{C}_4\text{H}_9\);
   - \( R^{25} \) is \(-\text{C}_2\text{H}_4\text{-}\);
   - \( A \) is a \( \text{OSO}_2\text{CF}_3 \) anion;
   - \( n \) is +2;
   - \( b \) is -1; and
   - \( y \) is 2 (complex 3).

5. The use of claim 1, wherein the complex has formulae I, and wherein,
   - \( M \) is \( \text{Au}^{3+} \);
   - \( X \) is a carbon atom;
   - \( R^1, R^2, R^3, R^4 \), and \( R^5 \) are each \(-\text{H}\);
- \( R^6 \) and \( R^7 \) are each \\
- \( A \) is a \( \text{OSO}_2\text{CF}_3 \) anion;  \\
- \( n \) is +1;  \\
- \( b \) is -1; and  \\
- \( y \) is 1 (complex 4).

6. The use of claim 1, wherein the complex has formulae I, and wherein,
- \( M \) is \( \text{Au}^{3+} \);  \\
- \( X \) is a carbon atom;  \\
- \( R^1, R^2, R^3, R^4, \) and \( R^5 \) are each \(-H\);  \\
- \( R^6 \) is \\
- \( R^7 \) is \\
- \( A \) is a \( \text{OSO}_2\text{CF}_3 \) anion; \\
- \( n \) is +1;  \\
- \( b \) is -1; and \\
- \( y \) is 1 (complex 5).

7. The use of claim 1, wherein the complex has formulae II, and wherein,
- \( M \) is \( \text{Au}^{3+} \);  \\
- \( X \) is a carbon atom;  \\
- \( R^8 \) is \\
- \( R^9 \) and \( R^{10} \) are each \(-H\);  \\
- \( R^{11} \) and \( R^{12} \) are each \(-\text{CH}_3\);  \\
- \( A \) is a \( \text{OSO}_2\text{CF}_3 \) anion;  \\
- \( n \) is +1;  \\
- \( b \) is -1; and
8. The use of claim 1, wherein the complex has formulae IV, and wherein,
- \( M \) is \( Au^{3+} \);
- \( X \) is a carbon atom;
- \( R_1^{26} \) and \( R_1^{29} \) are each ;
- \( R_1^{27} \), \( R_1^{28} \), \( R_1^{30} \) and \( R_1^{31} \) are each -H;
- \( R_1^{32} \) and \( R_1^{33} \) are each -C_4H_5;
- \( R_1^{34} \) is -CH_2-;
- \( A \) is a OSO_2CF_3 anion;
- \( n \) is +2;
- \( b \) is -1; and
- \( y \) is 2 (complex 7).

9. The use of claim 1, wherein the complex has formulae I, and wherein,
- \( M \) is \( Au^{3+} \);
- \( X \) is a carbon atom;
- \( R_1 \) is ;
- each pair of \( R_1^2 \) and \( R_1^3 \), and \( R_1^4 \) and \( R_1^5 \) is joined together to form ;
- \( R_1^6 \) and \( R_1^7 \) are each -CH_3;
- \( A \) is a OSO_2CF_3 anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 8).

10. The use of claim 1, wherein the complex has formulae III, and wherein,
- \( M \) is \( Au^{3+} \);
- \( X \) is a carbon atom;
- $R^{13}$ and $R^{18}$ are each
  - each pair of $R^{14}$ and $R^{15}$, $R^{16}$ and $R^{17}$, $R^{19}$ and $R^{20}$, $R^{21}$ and $R^{22}$, is joined together to

  form

- $R^{23}$ and $R^{24}$ are each $-C_4H_9$;
- $R^{25}$ is $-CH_2$;
- $A$ is a $OSO_2CF_3$ anion;
- $n$ is +2;
- $b$ is -1; and
- $y$ is 2 (complex 9).

11. The use of claim 1, wherein the complex has formulae II, and wherein,
- $M$ is $Au^{3+}$;
- $X$ is a carbon atom;

- $R^8$ is

- $R^9$ is $-NO_2$;
- $R^{10}$ is $-H$;
- $R^{11}$ and $R^{12}$ are each $-CH_3$;
- $A$ is a $OSO_2CF_3$ anion;
- $n$ is +1;
- $b$ is -1; and
- $y$ is 1 (complex 10).

12. The use of claim 1, wherein the complex has formulae I, and wherein,
- $M$ is $Pt^{2+}$;
- $X$ is a nitrogen atom;
- $R^1$, $R^2$, $R^3$, $R^4$, and $R^5$ are each $-H$;
- $R^6$ and $R^7$ are each $-CH_3$;
- $A$ is a $PF_6$ anion;
- $n$ is +1;
- b is -1; and
- y is 1 (complex 11).

13. The use of claim 1, wherein the complex has formulae I, and wherein,
   - M is Pt$^{2+}$;
   - X is a nitrogen atom;
   - $R^1$, $R^2$, $R^3$, $R^4$, and $R^5$ are each –H;
   - $R^6$ and $R^7$ are each –C$_2$H$_5$;
   - A is a PF$_6$ anion;
   - n is +1;
   - b is -1; and
   - y is 1 (complex 12).

14. The use of claim 1, wherein the complex has formulae I, and wherein,
   - M is Pt$^{2+}$;
   - X is a nitrogen atom;
   - $R^1$, $R^2$, $R^3$, $R^4$, and $R^5$ are each –H;
   - $R^6$ and $R^7$ are each –C$_3$H$_7$;
   - A is a PF$_6$ anion;
   - n is +1;
   - b is -1; and
   - y is 1 (complex 13).

15. The use of claim 1, wherein the complex has formulae I, and wherein,
   - M is Pt$^{2+}$;
   - X is a nitrogen atom;
   - $R^1$, $R^2$, $R^3$, $R^4$, and $R^5$ are each –H;
   - $R^6$ and $R^7$ are each –C$_4$H$_9$;
   - A is a PF$_6$ anion;
   - n is +1;
   - b is -1; and
   - y is 1 (complex 14).

16. The use of claim 1, wherein the complex has formulae III, and wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;
- R$^{13}$, R$^{14}$, R$^{15}$, R$^{16}$, R$^{17}$, R$^{18}$, R$^{19}$, R$^{20}$, R$^{21}$ and R$^{22}$ are each -H;
- R$^{23}$ and R$^{24}$ are each -C$_4$H$_9$;
- R$^{25}$ is -CH$_2$
- A is a PF$_6$ anion;
- n is +2;
- b is -1; and
- y is 2 (complex 15).

17. The use of claim 1, wherein the complex has formulae III, and wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;
- R$^{13}$, R$^{14}$, R$^{15}$, R$^{16}$, R$^{17}$, R$^{18}$, R$^{19}$, R$^{20}$, R$^{21}$ and R$^{22}$ are each -H;
- R$^{23}$ and R$^{24}$ are each -C$_4$H$_9$;
- R$^{25}$ is -C$_3$H$_6$
- A is a PF$_6$ anion;
- n is +2;
- b is -1; and
- y is 2 (complex 16).

18. The use of claim 1, wherein the complex has formulae I, and wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;

- R$^1$ is ;
- R$^2$, R$^3$, R$^4$, and R$^5$ are each -H;
- R$^6$ and R$^7$ are each -C$_3$H$_7$;
- A is a PF$_6$ anion;
- n is +1;
- b is -1; and
- y is 1 (complex 17).

19. The use of claim 1, wherein the complex has formulae I, and wherein,
- M is Pt\(^{2+}\);
- X is a nitrogen atom;

![Chemical Structure 1]

- \(R^1\) is 
- \(R^2\), \(R^3\), \(R^4\), and \(R^5\) are each -H;
- \(R^6\) and \(R^7\) are each \(-C_3H_7\);
- A is a PF\(^6\) anion;
- n is +1;
- b is -1; and
- y is 1 (complex 18).

20. The use of claim 1, wherein the complex has formulae III, and wherein,
- M is Pt\(^{2+}\);
- X is a nitrogen atom;

![Chemical Structure 2]

- \(R^{13}\) and \(R^{18}\) are each 
- \(R^{14}\), \(R^{15}\), \(R^{16}\), \(R^{17}\), \(R^{19}\), \(R^{20}\), \(R^{21}\) and \(R^{22}\) are each -H;
- \(R^{23}\) and \(R^{24}\) are each \(-C_4H_9\);
- \(R^{25}\) is -CH\(_2\);
- A is a PF\(^6\) anion;
- n is +2;
- b is -1; and
- y is 2 (complex 19).

21. The use of claim 1, wherein the complex has formulae III, and wherein,
- M is Pt\(^{2+}\);
- X is a nitrogen atom;

![Chemical Structure 3]

- \(R^{13}\) and \(R^{18}\) are each 
- \(R^{14}\), \(R^{15}\), \(R^{16}\), \(R^{17}\), \(R^{19}\), \(R^{20}\), \(R^{21}\) and \(R^{22}\) are each -H;
- \(R^{23}\) and \(R^{24}\) are each \(-C_4H_9\);
- $R^{25}$ is -CH$_2$
- A is a PF$_6$ anion;
- $n$ is +2;
- $b$ is -1; and
- $y$ is 2 (complex 20).

22. The use of claim 1, wherein the complex has formulae I, and wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;
- $R^1$ is -H;

- each pair of $R^2$ and $R^3$, and $R^4$ and $R^5$ is joined together to form ;
- $R^6$ and $R^7$ are each -C$_3$H$_7$;
- A is a PF$_6$ anion;
- $n$ is +1;
- $b$ is -1; and
- $y$ is 1 (complex 21).

23. The use of claim 1, wherein the complex has formulae III, and wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;
- $R^{13}$ and $R^{18}$ are each -H;
- each pair of $R^{14}$ and $R^{15}$, $R^{16}$ and $R^{17}$, $R^{19}$ and $R^{20}$, and $R^{21}$ and $R^{22}$ is joined together to form ;
- $R^{23}$ and $R^{24}$ are each -C$_4$H$_9$;
- $R^{25}$ is -CH$_2$
- A is a PF$_6$ anion;
- $n$ is +2;
- $b$ is -1; and
- $y$ is 2 (complex 22).

24. The use of claim 1, wherein the complex has formulae I, and wherein,
- M is Pt$^{2+}$;
- X is a nitrogen atom;
- \( R^1, R^2, R^3, R^4, \) and \( R^5 \) are each -H;
- \( R^6 \) is 
- \( R^7 \) is -C\(_3\)H\(_6\)OH;
- A is a PF\(_6\) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 23).

25. The use of claim 1, wherein the complex has formulae I, and wherein,
- \( M \) is Pt\(^{2+}\);
- X is a nitrogen atom;
- \( R^1, R^2 \) and \( R^3 \) are each -H;
- \( R^4 \) and \( R^5 \) are joined together to form 
- \( R^6 \) and \( R^7 \) are each C\(_3\)H\(_7\);
- A is a PF\(_6\) anion;
- \( n \) is +1;
- \( b \) is -1; and
- \( y \) is 1 (complex 24).

26. The use of claim 1, wherein the complex has formulae I, and wherein,
- \( M \) is Pt\(^{2+}\);
- X is a nitrogen atom;
- \( R^1, R^2 \) and \( R^3 \) are each -H;
- \( R^4 \) and \( R^5 \) are joined together to form 
- \( R^6 \) is C\(_4\)H\(_6\);
- \( R^7 \) is -C\(_2\)H\(_4\)OH;
- A is a PF\(_6\) anion;
- \( n \) is +1;
- \( b \) is -1; and
27. Use of a pharmaceutical composition comprising a cyclometalated N-heterocyclic carbene complex in manufacturing a medicament for treating cancer in a patient in need thereof, the cyclometalated N-heterocyclic carbene complex having one of the following formulae (I to IV):

or a pharmaceutically acceptable salt thereof, wherein,

- M is selected from the metal ion of Au\(^{3+}\) or Pt\(^{2+}\);

- X is selected from a carbon atom or a nitrogen atom;
- $R^1, R^8, R^{13}, R^{18}, R^{26},$ and $R^{25'}$ are each independently selected from the group consisting of $-H$, and

- $R^2, R^3, R^4, R^5, R^9, R^{10}, R^{14}, R^{15}, R^{16}, R^{17}, R^{19}, R^{20}, R^{21}, R^{22}, R^{27}, R^{28}, R^{31},$ and $R^{32}$ are each independently selected from the group consisting of $-H$ and $-NO_2$; or each pair of $R^2$ and $R^3$; $R^4$ and $R^5$; $R^9$ and $R^{10}$; $R^{14}$ and $R^{15}$; $R^{16}$ and $R^{17}$; $R^{19}$ and $R^{20}$; $R^{21}$ and $R^{22}$; $R^{27}$ and $R^{28}$; $R^{31}$ and $R^{32}$ is independently joined together to form

- $R^6, R^7, R^{11}, R^{12}, R^{23}, R^{24}, R^{32}$ and $R^{33}$ are each independently selected from the group consisting of -CH$_3$, -C$_2$H$_5$, -C$_3$H$_7$, -C$_4$H$_9$, -CH$_2$OH, -C$_2$H$_4$OH, -C$_3$H$_6$OH, -C$_4$H$_8$OH, and

- $R^{25}$ and $R^{34}$ are each independently selected from the group consisting of -CH$_2$-, -C$_2$H$_4$-, -C$_3$H$_6$- and -C$_4$H$_8$-;

- Each $A$ is independently a pharmaceutically acceptable counter-ion;

- $n$ is an integer ranging from 0 to +4;

- $b$ is an integer ranging from -4 to -1;

- $y$ is equal to the absolute value of $n/b$ when $n$ is >0; and

- $yA^b$ is absence when $n$ is equal to 0.

28. The use of claim 27, wherein the cancer is one or more of cervical epithelioid carcinoma, hepatocellular carcinoma, leukemia, nasopharyngeal carcinoma, breast carcinoma, melanoma, and lung carcinoma.
29. The use of claim 27, wherein the treatment comprises induction of cell death.

30. The use of claim 27, wherein the treatment comprises inhibition of cellular proliferation.

31. The use of claim 27, wherein the treatment comprises inhibition of topoisomerase.

32. The use of claim 27, wherein the treatment comprises poisoning of topoisomerase.

33. A method of making the cyclometalated N-heterocyclic carbene complex of claim 1, comprising:
   reacting a cyclometalated complex with a N-heterocyclic carbene compound to form the cyclometalated N-heterocyclic carbene complex of claim 1.

34. The method of claim 33 wherein the cyclometalated complex comprises a gold or platinum atom coordinated to a di-anionic substituted/ non-substituted 2,6-diphenylpyridine ligand or a mono-anionic substituted/ non-substituted 6-phenyl-2,2'-bipyridine ligand.

35. The use of anyone of claims 1-26, wherein the cancer is one or more of cervical epithelioid carcinoma, hepatocellular carcinoma, leukemia, nasopharyngeal carcinoma, breast carcinoma, melanoma, and lung carcinoma.
Fig. 5.
### INTERNATIONAL SEARCH REPORT

**A.  CLASSIFICATION OF SUBJECT MATTER**

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

**B.  FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07F, C08F, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DWPI, EPDOC, CNPAT, Chinese patent full text search system, Chinese medical patent search system, CNKI, CA: N-heterocyclic, hetero. ring, cyclic, carbene, metal, gold, platinum, cancer, tumor, leukemia, carcinoma, topoisomerase, proliferate, and their synonyms, STN structure query, Hong Kong university

**C.  DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No.</th>
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<td>WO 2009118475 A2 (SANOFI-AVENTIS ET AL (FR)) 1 October 2009 (01.10.2009) see all claims</td>
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☐ Further documents are listed in the continuation of Box C.  ☑ See patent family annex.

* Special categories of cited documents:

  - “A” document defining the general state of the art which is not considered to be of particular relevance
  - “E” earlier application or patent but published on or after the international filing date
  - “L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - “O” document referring to an oral disclosure, use, exhibition or other means
  - “P” document published prior to the international filing date but later than the priority date claimed

  “I” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

  “X” document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

  “Y” document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

  “&” document member of the same patent family

Date of the actual completion of the international search 21 January 2011 (21.01.2011).

Date of mailing of the international search report 17 Feb. 2011 (17.02.2011)

Name and mailing address of the ISA/CN
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088
Faesimile No. 86-10-62019451

Authorized officer WANG Jingjing
Telephone No. (86-10)62411985

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A. CLASSIFICATION OF SUBJECT MATTER

C07F 1/12 (2006.01)i
C07F 17A02 (2006.01)i
C07F 17A00 (2006.01)i
C08F 132/00 (2006.01)i
C08F 134/00 (2006.01)i
A61K 31/787 (2006.01)i
A61P 35/00 (2006.01)i
A61P 35/04 (2006.01)i
A61P 35/02 (2006.01)i

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