

COMPOUNDS FOR PHOTODYNAMIC THERAPY

Technical Field

5 The present invention generally relates to photodynamic therapy. In particular the present invention relates to novel transition metal-ligand complexes for use in photodynamic therapy.

Background

10 Photodynamic therapy (PDT) has been used widely in the treatment of a variety of cancers including, cutaneous cancers, Kaposi's sarcoma, esophageal cancer and non-small cell lung cancer.

15 PDT involves the localization of a photosensitive molecule (for example, a porphyrin) at a tumour site, followed by optical excitation of the molecule at a relatively long wavelength of for example $\lambda=650\text{nm}$.

Typically, upon optical excitation, the molecule is excited from a ground singlet state to an excited singlet state. The photoexcited singlet state of the dye molecule
20 then decays to a triplet state.

One of the few chemical species present in a tissue with a ground triplet state is molecular oxygen. When the photosensitizer and an oxygen molecule are in proximity,
25 an energy transfer takes place that permits the photosensitizer to revert to its ground singlet state, and create an excited singlet state oxygen molecule. Singlet oxygen is non-selectively cytotoxic. The cytotoxic action of the singlet oxygen ultimately kills cells present in a
30 tissue through apoptosis or necrosis. Transition metal complex based photo sensitizers may also cause DNA cleavage reaction leading to cell death.

The DNA cleavage reaction by transition metal complex based photosensitizers involving molecular oxygen ($^3\text{O}_2$) may proceed via two mechanistic pathways. In particular, the excited electronic state of the complex molecule, through efficient intersystem crossing, could generate excited triplet state of the complex that can activate molecular oxygen from its stable triplet($^3\text{O}_2$) to the reactive singlet ($^1\text{O}_2$) state by a type-II process. Alternatively, the redox active photo-activated complex molecule could reduce molecular oxygen to generate a reactive hydroxyl radical by a photo-redox mechanism.

However, existing PDT therapeutic approaches have a number of significant disadvantages. In particular, existing compounds for use in PDT are difficult to synthesise in large amounts; have low purity and aqueous solubility; and are only active in the wavelength of ~650nm, which is outside the optimal tissue transparency window of 700-1000nm, where tissue penetration is most effective.

From the foregoing, it will be appreciated that there exists a need in the art for a compound which is easy to synthesize in large amounts; has high purity and improved aqueous solubility, and is active in the wavelength of, 390 to 750nm, and especially so in the region of 600 to 700 nm where tissue penetration is effective.

Summary

According to a first aspect, there is provided a metal-ligand complex comprising a transition metal complexed with at least one Schiff base ligand comprising an additional nitrogen atom from a heterocycle and at

least one heteroaromatic nucleic acid intercalating moiety.

It is an advantage of the present disclosure that the aromatic heterocyclic moiety of the Schiff base ligand
5 increases the number of conjugated bonds. The increase in the number of double bonds is believed to increase the photosensitivity of the compound, particularly relative to known non heterocyclic Schiff base metal ligand complexes.

It is a further advantage of the disclosure that the
10 metal complex with the Schiff base ligand comprising an additional nitrogen atom from a heterocycle is stable in vivo, particularly relative to known Schiff base metal ligand complexes that do not contain additional nitrogen, such as sulphur-containing Schiff base metal ligand
15 complexes.

It is a further advantage of the disclosure that the metal complex with the Schiff base ligand comprising an additional nitrogen atom from a heterocycle is also easy to synthesise.

It is yet a further advantage of the disclosure that
20 the compound is also useful as an intraoperative adjunctive therapy. The use of the compound as an adjunctive therapy during surgery provides penetration at a site in a patient where the compound is required.

It is yet a further advantage of the disclosure that
25 the compound can be produced at a high purity and has improved aqueous solubility.

It is still a further advantage of the disclosure that the compounds are photochemically active in the
30 wavelength of, 390 to 750nm, but more specifically in the region of 600 to 700 nm, where tissue penetration is effective.

According to a second aspect, there is provided a pharmaceutical composition comprising the compound according to the first aspect, in admixture with a pharmaceutically acceptable carrier.

5 According to a third aspect, there is provided use of a compound or a composition as described above in the manufacture of a medicament for the treatment of cancer.

 According to a fourth aspect, there is provided use of a compound or a composition as described above in the
10 manufacture of a medicament for the treatment of a precancer.

 According to a fifth aspect, there is provided use of a compound or composition as described above in the manufacture of a medicament for the treatment of macular
15 degeneration.

 According to a sixth aspect, there is provided use of a compound or composition as described above in the manufacture of a medicament for the treatment of human papilloma virus (HPV) warts.

20 According to a seventh aspect, there is provided the use of a compound or composition as described above in the manufacture of a medicament for the treatment of a skin disorder.

 According to an eighth aspect, there is provided a
25 kit comprising a compound or a composition as described above, together with instructions for use.

Definitions

 The following are some definitions that may be
30 helpful in understanding the description of the present invention. These are intended as general definitions and should in no way limit the scope of the present invention

to those terms alone, but are put forth for a better understanding of the following description.

Unless the context requires otherwise or specifically stated to the contrary, integers, steps, or elements of
5 the invention recited herein as singular integers, steps or elements clearly encompass both singular and plural forms of the recited integers, steps or elements.

The term "transition metal" refers to any element in the d-block of the periodic table, which includes groups 3
10 to 12 on the periodic table.

The term "pharmaceutically acceptable carrier" is intended to include solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic agents, absorption delaying agents and absorption enhancing agents
15 and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the compound, use thereof in the therapeutic compositions and methods of treatment and
20 prophylaxis is contemplated. Supplementary active compounds may also be incorporated into the compositions according to the present invention. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity
25 of dosage.

"Dosage unit form" as used herein refers to physically discrete units suited as unitary dosages for the individual to be treated; each unit containing a predetermined quantity of compound(s) is calculated to
30 produce the desired therapeutic effect in association with

the required pharmaceutical carrier. The compound(s) may be formulated for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in an acceptable dosage unit. In the
5 case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

The term "precancer" refers to a lesion from which a
10 malignant tumor is presumed to develop in a significant number of instances and that may or may not be recognizable clinically or by microscopic changes in the affected tissue. In particular, without being bound by the following, a precancer may be classified by: (1)
15 evidence that the precancer is associated with an increased risk of cancer; (2) when a precancer progresses to cancer, the resulting cancer arises from cells within the precancer; (3) a precancer differs from the normal tissue from which it arises; (4) a precancer differs from
20 the cancer into which it develops, although it has some, but not all, of the molecular and phenotypic properties that characterize the cancer; (5) there is a method by which the precancer can be diagnosed.

The term "photosensitive" is to be construed as
25 meaning responsive to a light source. In the case of compounds according to the present disclosure, "photosensitive" is to be construed as meaning that upon optical excitation, the compound is excited from a ground singlet state to an excited singlet state.

30 The term "nucleic acid intercalating moiety" refers to part of a compound that can be inserted (intercalated) in between adjacent planes formed by double stranded

ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) nucleotide pairing. The term "nucleic acid intercalating moiety" in the context of this specification covers any molecular moiety comprising at least one essentially flat conjugated system, which is capable of co-stacking with bases of a nucleic acid. Preferably, a nucleic acid intercalating moiety has at least one essentially flat conjugated system, which is capable of co-stacking with bases of a nucleic acid or nucleic acid analogue. The nucleic acid intercalating moiety may comprise a chemical group selected from the group consisting of polyaromates and heteropolyaromates and even more preferably the intercalator essentially consists of a heteropolyaromate. Exemplary heteropolyaromates may consist of any suitable number of rings, such as 1, for example 2, such as 3, for example 4, such as 5, for example 6, such as 7, for example 8, such as more than 8. Furthermore heteropolyaromates may be substituted with one or more selected from the group consisting of hydroxyl, bromo, fluoro, chloro, iodo, mercapto, thio, cyano, alkylthio, heterocycle, aryl, heteroaryl, carboxyl, carboalkoyl, alkyl, alkenyl, alkynyl, nitro, amino, alkoxyl and amido. Other exemplary nucleic acid intercalating moieties may be selected from the group consisting of phenanthroline, phenazine, phenanthridine, acridones, oxalopyridocarbazoles, porphyrins, psoralens and any of the aforementioned intercalators substituted with one or more selected from the group consisting of hydroxyl, bromo, fluoro, chloro, iodo, mercapto, thio, cyano, alkylthio, heterocycle, aryl, heteroaryl, carboxyl, carboalkoyl, alkyl, alkenyl, alkynyl, nitro, amino, alkoxyl and/or amido. In some embodiments the "nucleic acid

intercalating moiety" may be a conjugated polycyclic heteroaromatic bidentate ligand.

The term "Schiff base" is intended to encompass a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group. The Schiff bases may be represented by the general formula $R_1R_2C=N-R_3$, where R_3 is an aryl or alkyl group.

The term "Schiff base ligand comprising an additional nitrogen atom from a heterocycle" or "nitrogen containing Schiff base" is intended to encompass a Schiff base coupled to one or more additional nitrogen atoms. That is, one or more nitrogen atoms other than the nitrogen atom present in the formula $R_1R_2C=N-R_3$ (hereinafter "additional nitrogen atom"). This additional nitrogen atom is the heteroatom present in a heterocyclic ring which is coupled to the Schiff base by an aliphatic group, preferably a short chain aliphatic group such as a methyl or ethyl or propyl or butyl group.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers, but not the exclusion of any other step or element or integer or group of elements or integers. Thus, in the context of this specification, the term "comprising" means "including principally, but not necessarily solely".

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications.

The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or
5 more of said steps or features.

The word "substantially" does not exclude "completely" e.g. a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from
10 the definition of the invention.

Unless specified otherwise, the terms "comprising" and "comprise", and grammatical variants thereof, are intended to represent "open" or "inclusive" language such that they include recited elements but also permit
15 inclusion of additional, unrecited elements.

As used herein, the term "about", in the context of concentrations of components of the formulations, typically means +/- 10% of the stated value, more typically +/- 5% of the stated value, more typically +/-
20 4% of the stated value, more typically +/- 3% of the stated value, more typically, +/- 2% of the stated value, even more typically +/- 1% of the stated value, and even more typically +/- 0.5% of the stated value.

Throughout this disclosure, certain embodiments may
25 be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be
30 considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, description of a range such as

from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Certain embodiments may also be described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the disclosure. This includes the generic description of the embodiments with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

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Disclosure of Optional Embodiments

Exemplary, non-limiting embodiments of a metal-ligand complex comprising a transition metal complexed with at least one Schiff base ligand comprising an additional nitrogen atom from a heterocycle and at least one heteroaromatic nucleic acid intercalating moiety will now be described.

Preferably, the heterocycle that provides an additional nitrogen atom to the Schiff base ligand is an aromatic heterocycle. In a preferred embodiment the compound is of the formula I:



wherein, M is a transition metal;
L is a Schiff base ligand comprising an additional nitrogen atom from a heterocycle,

B is a heteroaromatic nucleic acid intercalating moiety,

X is an anion, and

n is selected from 0 to 5.

5 In one embodiment, M is selected from the group consisting of Ti, V, Mn, Fe, Co, Ni, Cu, Zn, Tb, Eu, Gd, Dy, Lu, Zr, Nb, Mo, Te, Ru, Rh, Dd, Ag, Sn, Ta, W, Re, Os, Ir, Pt and Au.

Preferably, M is selected from the group consisting
10 of Cu(I), Cu(II), Ru, V, Ti, Zr, lanthanides, Fe(III), Pt(II), Pd(0) and Pd(II). Most preferably, M is Cu(II).

In one embodiment the Schiff base ligand comprising an additional nitrogen atom from a heterocycle comprises an imine nitrogen and an additional nitrogen atom from a
15 heterocycle. Preferably, the imine acts as a linker between a pair of aromatic groups. In one embodiment, at least one of the aromatic groups is heterocyclic while the other is salicyl group or 2-hydroxyacetophenonyl group. In a preferred embodiment the heterocyclic group
20 comprises pyridine or benzimidazole.

In one preferred embodiment, an imino-linker is coupled between the pyridine and the salicyl group.

In another preferred embodiment, an imino-linker is coupled between the pyridine and the 2-
25 hydroxyacetophenonyl group.

In another embodiment the Schiff base ligand containing additional nitrogen atom from a heterocycle is selected from N-salicyl-2-iminoethylpyridine (HSALIEP) or N-salicyl-2-iminomethylpyridine (HSALIMP) or N-salicyl-2-iminoethylbenzimidazole (HSALIEB) or N-salicyl-2-iminomethylbenzimidazole (HSALIMB) or N-(2-hydroxyacetophenonyl)-2-iminoethylpyridine (HHAPIEP) or N-

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(2-hydroxyacetophenonyl)-2-iminomethylpyridine (HHAPIMP) or
 N-(2-hydroxyacetophenonyl)-2-
 iminoethylbenzimidazole (HAPIEB), N-(2-
 hydroxyacetophenonyl)-2-iminomethylbenzimidazole (HAPIEB),

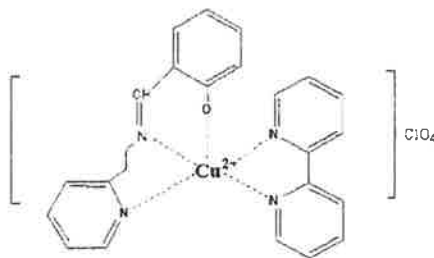
5 In another embodiment, the nucleic acid intercalating moiety comprises a heterocyclic aromatic intercalating moiety. Preferably, the heterocyclic aromatic intercalating moiety is selected from the group consisting of triazine, pyrazine, acridine, azepine, aziridine,
 10 benzodiazine, bipyridine, diazine, isoquinoline, , oxazine, phenanthridine, phenanthroline, piperazine, pteridine, purine, pyridine, pyrrole, pyrrolidine, quinoline, quinolizine, thiadiazine, thiazine, , and combinations thereof.

15 In a preferred embodiment, the nucleic acid intercalating moiety is selected from 2,2'-bipyridyl or 1,10-phenanthroline or 2,9-dimethyl-1,10-phenanthroline or dipyrido-[3,2-d:2',3'-f]-quinoxaline or dipyrido-[3,2-a:2',3'-c]-phenazine or their derivatives.

20 In another embodiment X is selected from the group consisting of ClO_4^- , NO_3^- , Cl^- , Br^- , I^- , PO_4^{3-} . Preferably, the anion is ClO_4^- .

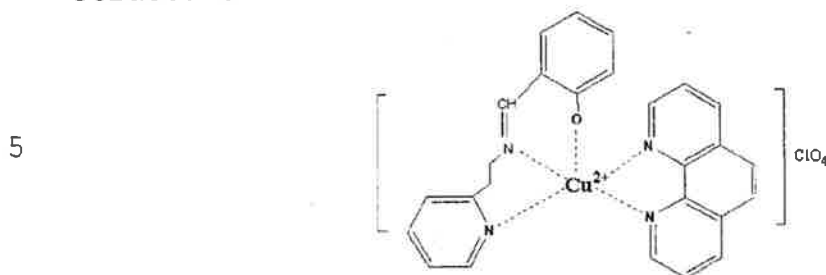
In a preferred embodiment, the compound has the structure:

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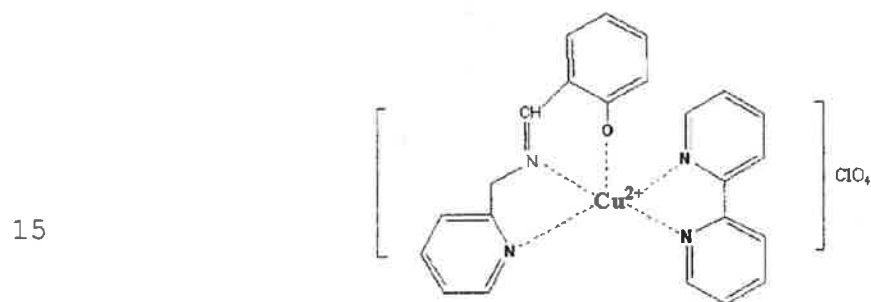


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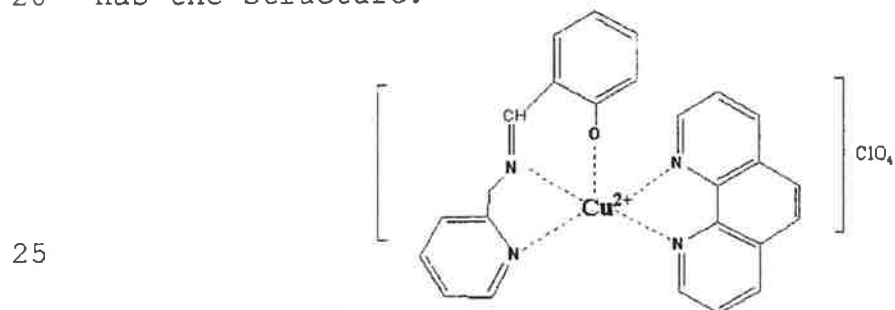
In another preferred embodiment the compound has the structure:



In yet another preferred embodiment the compound has the structure:

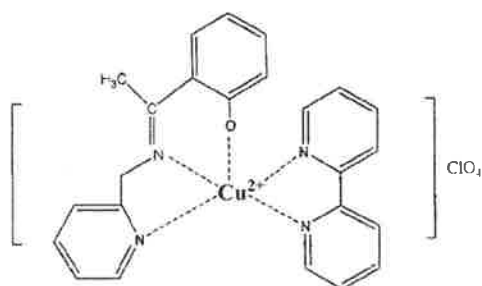


In still a further preferred embodiment the compound has the structure:



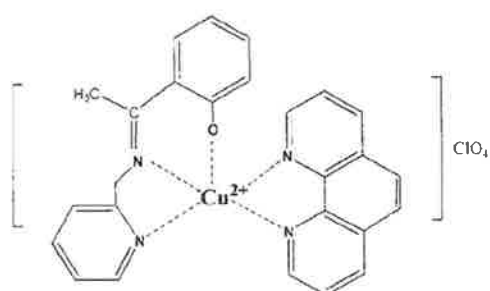
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In still a further preferred embodiment the compound has the structure:



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In still a further preferred embodiment the compound has the structure:

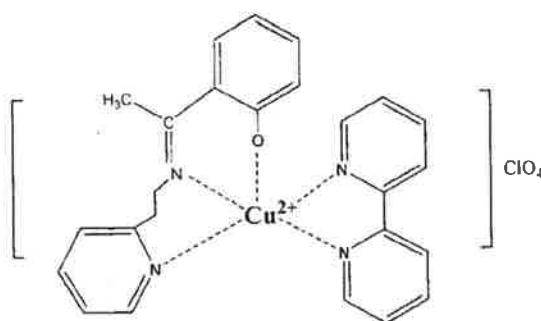


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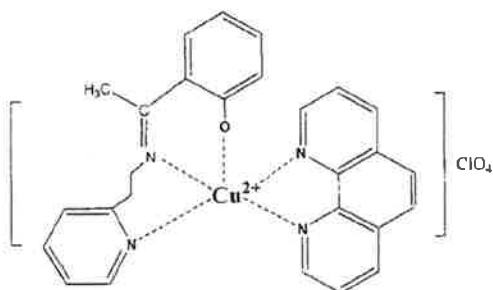
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In still a further preferred embodiment the compound has the structure:



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In still a further preferred embodiment the compound has the structure:



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Preferably, the compound is photosensitive to light of a wavelength of from about 10-1000nm. In a preferred embodiment the compound is photosensitive to light of a wavelength selected from 10-400nm, 390-750nm or 700-800nm. Preferably, the wavelength is from 390-750nm.

In another embodiment, there is provided a metal-ligand complex comprising a transition metal complexed

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with at least one nitrogen-containing Schiff base ligand and at least one nucleic acid intercalating moiety.

In another embodiment the present disclosure provides a pharmaceutical composition comprising the compound of formula I in admixture with a pharmaceutically acceptable carrier.

In accordance with the present invention, the compounds of the invention may be used in combination with other known treatment agents. Suitable agents are listed, for example, in the *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th Edition, 2006, the entire contents of which are incorporated herein by reference.

Combinations of active agents, including compounds of the invention, may be synergistic. Combinations of active agents may be co-administered either simultaneously or sequentially.

Convenient modes of administration include injection (subcutaneous, intravenous, etc.), oral administration, transdermal application, topical creams or gels or powders, biodegradable implant, or rectal administration. Depending on the route of administration, the formulation and/or compound may be coated with a material to protect the compound from the action of enzymes, acids and other natural conditions which may inactivate the therapeutic activity of the compound. The compound may also be administered parenterally or intraperitoneally.

Pharmaceutical compositions suitable for injection include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. Ideally, the composition is stable under the

conditions of manufacture and storage and may include a preservative to stabilise the composition against the contaminating action of microorganisms such as bacteria and fungi.

5 In one embodiment, the compound may be administered by injection. In the case of injectable solutions, the carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention
10 of the action of microorganisms can be achieved by including various anti-bacterial and/or anti-fungal agents. Suitable agents are well known to those skilled in the art and include, for example, parabens, chlorobutanol, phenol, benzyl alcohol, ascorbic acid, thimerosal, and the like. In many cases, it may be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent
20 which delays absorption, for example, aluminium monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the compound in the required amount in an appropriate solvent with one or a combination of
30 ingredients enumerated above, as required, followed by filtered sterilisation. Generally, dispersions are prepared by incorporating the compound into a sterile

vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above.

Preferably, the pharmaceutical composition may further include a suitable buffer to minimise acid
5 hydrolysis. Suitable buffer agents are well known to those skilled in the art and include, but are not limited to, phosphates, citrates, carbonates and mixtures thereof.

Single or multiple administrations of the pharmaceutical composition according to the invention may
10 be carried out. One skilled in the art would be able, by routine experimentation, to determine effective, non-toxic dosage levels of the compound and/or composition of the invention and an administration pattern which would be suitable for treating the diseases to which the compounds
15 and compositions are applicable.

Further, it will be apparent to one of ordinary skill in the art that the optimal course of treatment, such as the number of doses of the compound or composition of the invention given per day for a defined number of days, can
20 be ascertained using convention course of treatment determination tests.

In a preferred embodiment the compounds of the present disclosure are soluble in a solvent selected from the group consisting of water, ethanol and propylene
25 glycol. Most preferably, the compounds can be dissolved in a solvent at a concentration selected from the group consisting of about 0.05mM to 5mM; about 0.1mM to 4mM; about 0.2mM to 3mM; about 0.3mM to 2mM; about 0.4mM to 1.5mM; about 0.5mM to 1mM; about 0.6mM to 1mM; about 0.7mM
30 to 1mM; about 0.8mM to 1mM and 0.9mM to 1mM. Preferably, the concentration is 1mM.

Generally, an effective dosage per 24 hours may be in the range of about 0.0001 mg to about 1000 mg per kg body weight; suitably, about 0.001 mg to about 750 mg per kg body weight; about 0.01 mg to about 500 mg per kg body weight; about 0.1 mg to about 500 mg per kg body weight; about 0.1 mg to about 250 mg per kg body weight; or about 1.0 mg to about 250 mg per kg body weight. More suitably, an effective dosage per 24 hours may be in the range of about 1.0 mg to about 200 mg per kg body weight; about 1.0 mg to about 100 mg per kg body weight; about 1.0 mg to about 50 mg per kg body weight; about 1.0 mg to about 25 mg per kg body weight; about 5.0 mg to about 50 mg per kg body weight; about 5.0 mg to about 20 mg per kg body weight; or about 5.0 mg to about 15 mg per kg body weight.

Alternatively, an effective dosage may be up to about 500mg/m². For example, generally, an effective dosage is expected to be in the range of about 25 to about 500mg/m², about 25 to about 350mg/m², about 25 to about 300mg/m², about 25 to about 250mg/m², about 50 to about 250mg/m², and about 75 to about 150mg/m².

There is provided the use of a compound or composition as described above in the manufacture of a medicament for the treatment of cancer.

The cancer may be selected from the group consisting of skin cancer, lung cancer, stomach cancer, prostate cancer, cervical cancer, vulvar cancer, penile cancer and pancreatic cancer.

In a preferred embodiment, the skin cancer is selected from squamous cell carcinoma, basal cell carcinoma and melanoma.

Preferably the lung cancer is non-small cell lung cancer or small cell lung cancer.

In a preferred embodiment the cancer is located on the head or neck of a subject, including but not limited to
5 tumours or cancers of the lip, mouth, tongue, nasal cavities, throat and thorax. Advantageously, the compound according to the disclosure provides an alternative treatment for such cancers and ameliorates the need for
10 disfiguring and debilitating surgery, the effects of which cannot be fully remedied by cosmetic and reconstructive surgery. It is a further advantage of the disclosure that even if surgery is retained as the preferred treatment for such cancers, the compounds described herein may be used intraoperatively to improve patient outcomes.

15 There is provided the use of a compound or composition as described above in the manufacture of a medicament for the treatment of a precancer. The precancer may be selected from Bowen's disease (squamous cell carcinoma in situ) actinic keratosis, actinic cheilitis or Barrett's
20 oesophagus.

There is provided the use of a compound or composition as described above in the manufacture of a medicament for the treatment of macular degeneration. Preferably, the macular degeneration is wet macular degeneration.

25 There is provided the use of a compound or composition as described above in the manufacture of a medicament for the treatment of human papilloma virus (HPV) warts. The warts may be selected from the group consisting of common warts (*Verruca vulgaris*); flat warts (*Verruca Planae*);
30 filiform warts; plantar warts (*Verruca pedis*); mosaic warts; genital warts (*Condyloma acuminatum*, *Verruca acuminata*) and periugual warts.

There is provided the use of a compound or composition as described above in the manufacture of a medicament for the treatment of a skin disorder. Preferably, the skin disorder is selected from acne vulgaris, rosacea, sun damage, oily skin, enlarged sebaceous glands, wrinkles, skin rejuvenation (anti-aging), hidradenitis suppurativa, psoriasis, atopic dermatitis and age spots.

In another embodiment there is provided a kit comprising the compound or composition as described above together with instructions for use. Preferably, the kit may also contain one or more further therapeutic agents.

In a further preferred embodiment, there is provided a photodynamic therapy kit comprising the compound or composition as described above together with instructions for use. Preferably, the kit may contain one or more further therapeutic agents.

Brief Description of Drawings

The accompanying drawings illustrate a disclosed embodiment and serve to explain the principles of the disclosed embodiment. However, it is to be understood that the drawings are designed merely for the purposes of illustration, and are not to be construed as a definition of the limits of the invention.

Figure 1 is an ORTEP (Oak Ridge Thermal-Ellipsoid Plot Program) view of compound [Cu(SALIMP)(phen)](ClO₄).H₂O.C₂H₅OH in accordance with the present disclosure;

Figure 2 is an absorption spectra of [Cu(SALIMP)(bipy)](compound **III**) in 5mM Tris-HCl, 50mM NaCl, (pH7.2) upon addition of CT-DNA. [Cu] = 0.3 mM,

[DNA] = (0- 2.4) mM. Arrow shows the absorbance changing upon increasing DNA concentrations. Inset: plots of $[DNA]/(\epsilon_a - \epsilon_s)$ vs. [DNA] for the titration of DNA with the complex. Experimental data points; full lines, linear fitting of the data;

Figure 3 is a gel electrophoresis diagram showing the extent of cleavage of SC pUC19 DNA (0.5 μ g) by compound **I**, **II**, **III** and **IV** under different light conditions by compounds according to the disclosure, and Figure 4. Gel electrophoresis diagram showing the extent of cleavage of SC pUC19 DNA (0.5 μ g) by compound **V**, **VI**, **VII** and **VIII** under different light conditions.

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Examples

Non-limiting examples of the invention will be further described in greater detail by reference to specific Examples, which should not be construed as in any way limiting the scope of the invention.

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Synthesis route and purification process

1). Synthesis of Schiff base ligands (HL)

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N-salicylidine-2-iminoethylpyridine (HSALIEP) was prepared by refluxing salicylaldehyde and 2-aminoethyl pyridine in a 1:1 molar ratio in dry ethanol. The ligand was used directly in the next step without isolation.

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N-salicylidine-2-iminomethylpyridine (HSALIMP) was prepared by refluxing salicylaldehyde and 2-picoly l amine in a 1:1 molar ratio in dry ethanol. The ligand was used directly in the next step without isolation.

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N-(2-hydroxyacetophenonyl)-2-iminomethylpyridine (HHAPIMP) was prepared by refluxing 2-hydroxy acetophenone and 2-picoly l amine in a 1:1 molar ratio in dry ethanol. The ligand was used directly in the next step without isolation.

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N-(2-hydroxyacetophenonyl)-2-iminoethylpyridine (HHAPIEP) was prepared by refluxing 2-hydroxy acetophenone and 2-aminoethyl pyridine in a 1:1 molar ratio in dry ethanol. The ligand was used directly in the next step without isolation.

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2). Synthesis of binary complex [Cu(L)](ClO₄).nH₂O

[Cu(SALIEP)](ClO₄).0.5H₂O

20 HSALIEP solution in dry ethanol (8 mmol) was added drop wise to the dry ethanolic solution of copper(II) perchlorate (8 mmol). The resulting mixture was stirred for 1 hour at room temperature. Dark green solid precipitated was filtered, washed with ethanol and dried in air.

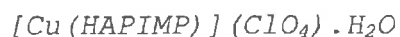
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[Cu(SALIMP)](ClO₄).H₂O

HSALIMP solution in dry ethanol (2.5 mmol) was added drop wise to the dry ethanolic solution of copper(II) perchlorate (2.5 mmol). The resulting mixture was stirred for 1 hour at room temperature. Dark green solid

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precipitated was filtered, washed with ethanol and dried in air.



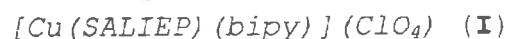
5 HHAPIMP solution in dry ethanol (10 mmol) was added drop wise to the dry ethanolic solution of copper(II) perchlorate (10 mmol). The resulting mixture was refluxed for 1 hour. Dark bluish green solid precipitated was filtered, washed with ethanol and dried in air.

10



HHAPIEP solution in dry ethanol (10 mmol) was added drop wise to the dry ethanolic solution of copper(II) perchlorate (10 mmol). The resulting mixture was refluxed
15 for 1 hour. Dark green solid precipitated was filtered, washed with ethanol and dried in air.

3). Synthesis of ternary complexes $[\text{Cu}(\text{L})(\text{B})](\text{ClO}_4) \cdot n\text{H}_2\text{O}$, where B = 2,2'-bipyridine (bipy) or 1,10-phenanthroline (phen)
20



To 10ml ethanolic solution of 0.397g (1.0 mmol) $[\text{Cu}(\text{SALIEP})](\text{ClO}_4) \cdot 0.5\text{H}_2\text{O}$, 0.156 g (1.0 mmol) 2, '2'
25 bipyridine dissolved in 10 ml of ethanol was added dropwise. The resultant mixture was refluxed for 1hour. The green crystalline solid that was separated out was filtered, washed with ethanol and air dried. The compound was recrystallised from ethanol. Yield 75%. (Found: C,
30 53.02; H, 3.90; N, 10.05. Calc. for $\text{C}_{24}\text{H}_{21}\text{ClN}_4\text{O}_5\text{Cu}$: C,

52.94; H, 3.86; N, 10.29%). IR, cm^{-1} (KBr disc): 1626 vs (C=N).

[Cu(SALIEP)(phen)](ClO₄) (II)

5 To 10ml ethanolic solution of 0.198g (0.5 mmol) [Cu(SALIEP)](ClO₄).0.5H₂O, 0.09 g (0.5 mmol) 1,10-phenanthroline dissolved in 10 ml of ethanol was added drop wise. The resultant mixture was refluxed for 1hour. The green crystalline solid was separated out in 75% yield.
10 The solid was filtered, washed with ethanol and air dried. The compound was recrystallised from ethanol. The green crystalline solid that was separated out was filtered, washed with ethanol and air dried. The compound was recrystallised from ethanol. Yield 75%. (Found: C, 54.60; H, 3.73; N, 9.62. Calc. for C₂₆H₂₁ClN₄O₅Cu: C, 54.92; H, 3.69; N, 9.85%). IR, cm^{-1} (KBr disc): 1625 vs (C=N).

[Cu(SALIMP)(bipy)](ClO₄) (III)

20 To 10ml ethanolic solution of 0.117g (0.3 mmol) [Cu(SALIMP)](ClO₄).H₂O, 0.0468 g (0.3 mmol) 2, 2'-bipyridine dissolved in 10 ml of ethanol was added drop wise. The resultant mixture was stirred at room temperature for 30 minutes. The green crystalline solid
25 that was separated out was filtered, washed with ethanol and air dried. The compound was recrystallised from ethanol. Yield 85%. (Found: C, 52.16; H, 3.63; N, 10.31. Calc. for C₂₃H₁₉ClN₄O₅Cu: C, 52.07; H, 3.58; N, 10.56%). IR, cm^{-1} (KBr disc): 1631 vs (C=N).

30

[Cu(SALIMP)(phen)](ClO₄).H₂O. C₂H₅OH (IV)

To 10ml ethanolic solution of 0.117g (0.3 mmol) [Cu(SALIMP)](ClO₄).H₂O, 0.054 g (0.3 mmol) 1,10-phenanthroline dissolved in 10 ml of ethanol was added drop wise. The resultant mixture was stirred at room temperature for 30 minutes. The green crystalline solid that was separated out was filtered, washed with ethanol and air dried. The compound was recrystallised from ethanol. Yield 85%. (Found: C, 52.24; H, 3.66; N, 8.91. Calc. for C₂₇H₂₇ClN₄O₇Cu: C, 52.42; H, 3.88; N, 9.06%). IR, cm⁻¹(KBr disc): 1633 vs (C=N).

[Cu(HAPIMP)(bipy)](ClO₄) (V)

To 10ml methanolic solution of 0.406g (1.0 mmol) [Cu(HAPIMP)](ClO₄).H₂O, 0.156 g (1.0 mmol) 2, 2' bipyridine dissolved in 10 ml of methanol was added drop wise. The resultant mixture was stirred at room temperature for 30 minutes. The green crystalline solid was separated out. The solid was filtered, washed with methanol and air dried. The compound was recrystallised from methanol. Yield 85%. (Found: C, 53.01; H, 3.90; N, 10.08. Calc. for C₂₄H₂₁ClN₄O₅Cu: C, 52.94; H, 3.86; N, 10.29%). IR, cm⁻¹(KBr disc): 1604 vs (C=N).

[Cu(HAPIMP)(phen)](ClO₄) (VI)

To 10ml methanolic solution of 0.406g (1.0 mmol) [Cu(HAPIMP)](ClO₄).H₂O, 0.180 g (1.0 mmol) 1, 10 phenanthroline dissolved in 10 ml of methanol was added drop wise. The resultant mixture was stirred at room temperature for 30 minutes. The green crystalline solid was separated out. The solid was filtered, washed with methanol and air dried. The compound was recrystallised

from methanol. Yield 83%. (Found: C, 54.98; H, 3.73; N, 9.77. Calc. for $C_{26}H_{21}ClN_4O_5Cu$: C, 54.92; H, 3.69; N, 9.85%). IR, cm^{-1} (KBr disc): 1599 vs (C=N).

5 **[Cu(HAPIEP)(bipy)](ClO₄) (VII)**

0.402 g (1.0 mmol) of [Cu(HAPIEP)](ClO₄) was dissolved in 60 ml of warm methanol. To this solution 0.156 g (1.0 mmol) 2, 2' bipyridine dissolved in 10 ml of methanol was added drop wise. The resultant solution was refluxed for 1
10 hour. The solvent was evaporated by rotary evaporation. The green crystalline solid separated was filtered, washed with methanol and air dried. The compound was recrystallised from methanol. Yield 75%. (Found: C, 53.82; H, 4.16; N, 9.97. Calc. for $C_{25}H_{23}ClN_4O_5Cu$: C, 53.76; H,
15 4.12; N, 10.03%). IR, cm^{-1} (KBr disc): 1599 vs (C=N).

[Cu(HAPIEP)(phen)](ClO₄) (VIII)

0.201 g (0.05 mmol) of [Cu(HAPIEP)](ClO₄) was dissolved in 60 ml of warm methanol. To this solution 0.180 g (0.05
20 mmol) 1, 10 phenanthroline dissolved in 10 ml of methanol was added drop wise. The resultant solution was refluxed for 1 hour. The solvent was evaporated by rotary evaporation. The green crystalline solid separated was filtered, washed with methanol and air dried. The compound
25 was recrystallised from methanol. Yield 75%. (Found: C, 55.73; H, 4.01; N, 9.57. Calc. for $C_{27}H_{23}ClN_4O_5Cu$: C, 55.67; H, 3.95; N, 9.62%). IR, cm^{-1} (KBr disc): 1599 vs (C=N).

30 **Crystal structure of compound**
[Cu(SALIMP)(phen)](ClO₄).H₂O.C₂H₅OH.

The crystal structure of compound [Cu(SALIMP)(phen)](ClO₄).H₂O.C₂H₅OH was obtained by single crystal X-ray diffraction technique. Single crystal was obtained slow evaporation of ethanolic solution of the complex. The diffraction experiments were carried out on a Bruker SMATR CCD diffractometer with a MoK α sealed tube. The program SMART was used for collecting frames of data, indexing reflection, and determining lattice parameters; SAINT was used for integration of the intensity of reflections and scaling. SADABS was used for absorption correction, and SHELXTL was used for space group and structure determination and least refinement on F². Selected crystallographic data of experimental details are compiled in Table 2.

15

Table 1. Crystal data and structure refinement for compound [Cu(SALIMP)(phen)](ClO₄).H₂O (IV).

	Identification code	9295a
	Empirical formula	C ₂₇ H _{25.50} Cl Cu N ₄ O _{6.25}
20	Formula weight	605.00
	Temperature	223(2) K
	Wavelength	0.71073 Å
	Crystal system	Orthorhombic
	Space group	Pbca
25	Unit cell dimensions	a = 20.0374(7) Å $\angle$ = 90°. b = 12.4850(5) Å $\angle$ = 90°. c = 20.9085(8) Å $\angle$ = 90°.
	Volume	5230.6(3) Å ³
	Z	8
30	Density (calculated)	1.537 Mg/m ³
	Absorption coefficient	0.989 mm ⁻¹
	F(000)	2492
	Crystal size	0.60 x 0.20 x 0.12 mm ³
	Theta range for data collection	1.95 to 27.50°.

	Index ranges	-26<=h<=20, -15<=k<=16, -
	27<=l<=27	
	Reflections collected	35452
	Independent reflections	6000 [R(int) = 0.0486]
5	Completeness to theta = 27.50°	99.9 %
	Absorption correction	Semi-empirical from equivalents
	Max. and min. transmission	0.8905 and 0.5884
	Refinement method	Full-matrix least-squares on F ²
	Data / restraints / parameters	6000 / 2 / 357
10	Goodness-of-fit on F ²	1.044
	Final R indices [I>2sigma(I)]	R1 = 0.0545, wR2 = 0.1525
	R indices (all data)	R1 = 0.0688, wR2 = 0.1618
	Largest diff. peak and hole	0.749 and -0.539 e.Å ⁻³

15

20 **Table 2. Some selected bond distances (Å) and bond angles (°) of compound [Cu(SALIMP)(phen)](ClO₄).H₂O (IV)**

	Cu(1)-O(1)	1.921(2)
	Cu(1)-N(2)	1.940(2)
25	Cu(1)-N(1)	2.033(3)
	Cu(1)-N(3)	2.036(3)
	Cu(1)-N(4)	2.253(3)
	O(1)-Cu(1)-N(2)	93.53(10)
	O(1)-Cu(1)-N(1)	159.99(10)
30	N(2)-Cu(1)-N(1)	82.07(11)
	O(1)-Cu(1)-N(3)	88.29(10)
	N(2)-Cu(1)-N(3)	177.30(11)
	N(1)-Cu(1)-N(3)	96.89(10)
	O(1)-Cu(1)-N(4)	106.92(9)
35	N(2)-Cu(1)-N(4)	99.44(10)
	N(1)-Cu(1)-N(4)	93.08(10)

N(3)-Cu(1)-N(4) 78.11(10)

DNA binding study by absorption titration

The DNA binding experiments were performed at room
5 temperature. The DNA concentration per nucleotide was
determined by absorption spectroscopy using the molar
absorption coefficient ($6600\text{M}^{-1}\text{cm}^{-1}$) at 260 nm. Absorption
titration experiments of Cu(II) complexes (**I - VIII**) in
buffer (5mM Tris-HCl, 50mM NaCl, pH7.2) were performed by
10 using a fixed copper concentration to which increments of
the DNA was added to a maximum ratio of 8:1 [DNA]:[copper
complex]. Copper-DNA solutions were allowed to incubate
for 10 minutes before the absorption spectra were recorded
(see Figure 2).

15

The intrinsic binding constant K_b of copper (II) complexes
(**I - VIII**) to DNA was calculated using the following the
equation:

20
$$[\text{DNA}] / (\epsilon_a - \epsilon_f) = [\text{DNA}] / (\epsilon_b - \epsilon_f) + 1/[K_b(\epsilon_b - \epsilon_f)]$$

where [DNA] is the concentration of DNA in base pairs, ϵ'_a ,
 ϵ_f and ϵ_b are the apparent, free, and bound metal complex
extinction coefficients, respectively. In plots of
25 $[\text{DNA}]/(\epsilon_a - \epsilon_f)$ versus [DNA], K_b is given by the ratio of
slope to the intercept.

Absorption titration method was used to monitor the
interaction of the complexes **I - VIII** with CT DNA.
Intercalation of a complex to DNA generally results in
30 hypochromism and red shift (bathochromism) of the
absorption band due to strong stacking interaction of

aromatic chromophore of the ligand and the base pairs of DNA. The extent of hypochromism thus gives an estimate of the strength of an intercalative binding.

Figure 2 shows the decrease in absorbance spectra of compound **III** with increasing amount of CT DNA which correlates with intercalation of compound **III** with the CT DNA. The similar spectral changes were observed for all eight ternary copper (II) complexes (compounds **I** - **VIII**). The ternary copper(II) complexes with 1, 10-phenanthroline as DNA binder (complex **II**, **IV**, **VI** and **VIII**) show higher extent of hypochromism than the ternary copper(II) complexes with 2, 2' bipyridine as DNA binder (complex **I**, **III**, **V** and **VII**) because of higher binding ability of 1, 10-phenanthroline at the minor groove of DNA. The intrinsic equilibrium DNA binding constant (K_b) values of the complexes follow the same order as observed in the trend of hypochromism.

DNA cleavage study by gel electrophoresis

The DNA cleavage activity of the complexes was studied using SC pUC19 DNA in a medium of Tris-HCl / NaCl buffer with a complex concentration of 200 μ M. The cleavage reactions were carried out under aerobic conditions and were monitored by agarose gel electrophoresis. DNA cleavage in both dark and in the presence of light was carried out. The photo-induced DNA cleavage activity of the complexes was studied after irradiation of complexes with monochromatic light of different wavelength using Luzchem photoreactor and lamps for 30 minutes exposure and monitored by gel electrophoresis (Figure. 3 and 4). Table 3 shows the specifications of light used:

Table 3:

Light	Specification
LZC-UVA	UVA lamp centered at ~350 nm
LZC-420	Lamp centered at ~420 nm.
LZC-VIS	Cool white fluorescent tubes with Red sleeve filter - cuts off at 600 nm for "red only" irradiation.

When circular plasmid DNA is subjected to electrophoresis, relatively fast migration is observed for the intact supercoiled DNA (SC, type I). If scission occurs on one strand (nicking), the super coiled DNA will relax to generate a slower moving open circular form (NC, type II). If both strands are cleaved, a linear form (type III) that migrates between type I and type II will be generated.

The four compounds (**I**, **II**, **III** and **IV**) were found DNA cleavage inactive under dark condition. All the four compounds however show strong photo induced DNA cleavage activity in the presence of UVA (~350 nm) light and significant photo induced DNA cleavage activity in the presence of visible wavelength of light (~ 600 nm) where conversion of type I (super coiled, SC) to type II (nicked circular) was observed. As can be seen from the results in **Table 4** and **Figure 3**, the results of lanes 2, 5, 7 and 10-12 show the best results compared to the control in lane 1. Compound **IV** was found to show strong photo induced DNA cleavage activity in the presence of all three wavelength of light used in the experiment.

Table 4: Cleavage of pUC19 DNA(0.5µg) by complexes **I**, **II**, **III** and **IV** under different reaction conditions.

Lane number	Reaction Condition	%Form-I (SC)	%Form-II (NC)
-------------	--------------------	--------------	---------------

1	DNA control	94	6
2	DNA+ I , (UVA)	11	89
3	DNA+ I , (420nm)	64	36
4	DNA+ I , (Vis)	70	30
5	DNA+ II , (420nm)	34	66
6	DNA+ II , (Vis)	67	33
7	DNA+ III , (UVA)	10	90
8	DNA+ III , (420nm)	63	37
9	DNA+ III , (Vis)	43	57
10	DNA+ IV , (UVA)	1	99
11	DNA+ IV , (420nm)	2	98
12	DNA+ IV , (Vis)	5	95

Control experiments with SC DNA with the four compounds (**V**, **VI**, **VII** and **VIII**) in dark do not show any appreciable DNA cleavage activity. All the four compounds are found to be efficient photo cleaver of DNA in the presence of UVA (~350 nm) light and have significant photo induced DNA cleavage activity in the presence of visible wavelength of light (~ 600 nm). A conversion of type I (super coiled, SC) to type II (nicked circular) and type III (linear form) was observed for all four compounds (**V**, **VI**, **VII** and **VIII**) in the presence of UVA (~350 nm) light.

Table 5: Different reaction conditions used to study cleavage of pUC19 DNA(0.5µg) by complexes **V**, **VI**, **VII** and **VIII** using Gel electrophoresis

Lane number	Reaction Condition
1	DNA control
2	DNA+ V (UVA)
3	DNA+ V (420nm)
4	DNA+ V (Vis)
5	DNA+ VI (UVA)
6	DNA+ VI (420nm)
7	DNA+ VI (Vis)
8	DNA+ VII (UVA)
9	DNA+ VII (420nm)

10	DNA+VII (Vis)
11	DNA+VIII (UVA)
12	DNA+VIII (420nm)
13	DNA+VIII (Vis)

Solubility testing of compounds I-IV in various solvent systems commonly used for formulation.

5 Table 6 shows the solubility of compounds in accordance with the present disclosure in various solvents. The poor solubility of compound IV in all the solvent systems can be explained from its crystal structure. Crystal structure of compound **IV** (Figure 1) shows the asymmetric unit contains one cation $C_{25}H_{19}N_4O_4Cu$, one anion ClO_4^- , one ethanol and a quarter water molecule. The Hydrogen bonds present in compound **IV** are listed in Table 7. Hydrogen bonding between the solvent of crystallization C_2H_5OH and the anion ClO_4^- makes the compound sparingly soluble in different solvents. The solubility of the compound can be improved by exchanging the anion ClO_4^- with other anions such as NO_3^- or Br^- . All of the compounds are capable of providing a 1mM solution, even when only sparingly soluble.

20

Table 6.

Solvents	Compound I	Compound II	Compound III	Compound IV
H ₂ O	Soluble	Soluble	Soluble	Sparingly Soluble
H ₂ O:Ethanol 1:1	Soluble	Very Soluble	Soluble	Sparingly Soluble
90% Ethanol	Soluble	Very Soluble	Soluble	Sparingly Soluble
100% Ethanol	Very Soluble	Very Soluble	Soluble	Sparingly Soluble
Ethanol:	Soluble	Very	Sparingly	Sparingly

Propyleneglycol 60:40		Soluble	Soluble	Soluble
100% Propyleneglycol	Soluble	Soluble	Soluble	Sparingly Soluble

Table 7. **Hydrogen bond distances (Å) and bond angles (°) of compound [Cu (SALIMP) (phen)] (ClO₄) .H₂O (IV)**

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1S)- H(1S)...O(4)	0.82	2.32	3.096(6)	158.9
O(1S)- H(1S)...O(2)	0.82	2.59	3.263(5)	140.3

5

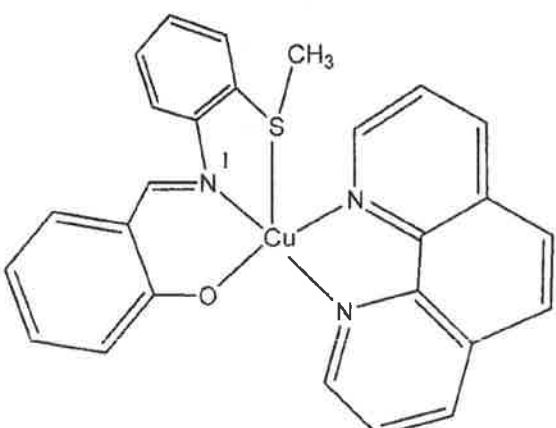
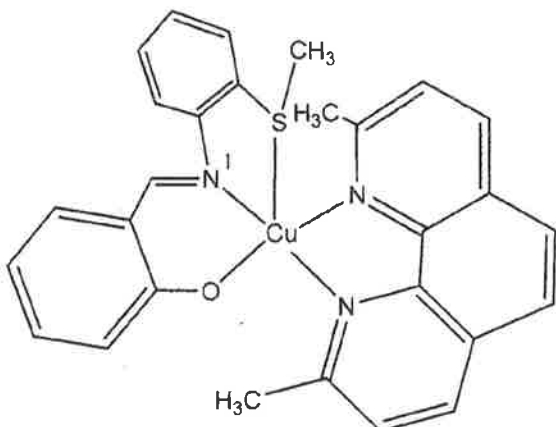
10 **Comparative study on the stability of sulphur containing Schiff base metal ligand complexes and metal complex with Schiff base ligand containing additional nitrogen atom from a heterocycle**

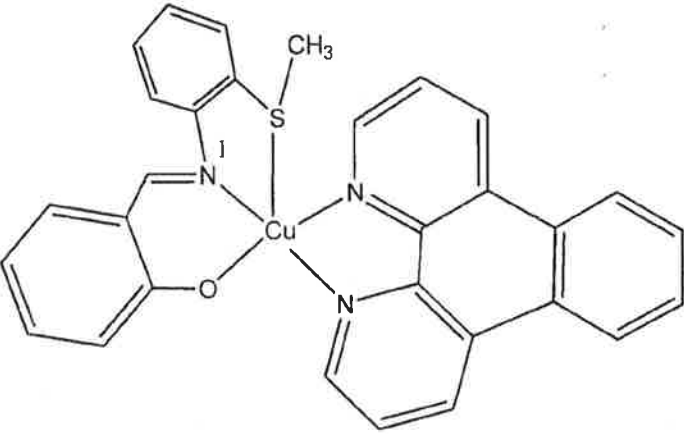
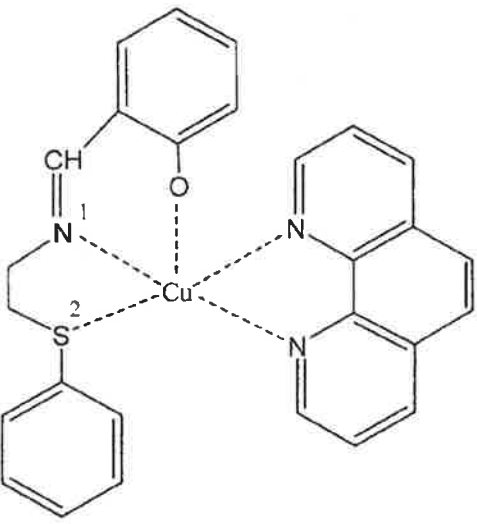
From Table 8 below it can be seen that imine C=N infra red stretching frequencies in the metal complexes with Schiff base ligand comprising an additional nitrogen atom from a heterocycle; compounds **I-IV** of the present disclosure are higher than those of sulphur containing Schiff base metal ligand complexes (a-e) reported in the literature. Higher stretching frequencies demonstrate greater bond strength of C=N bond which indicate that the C=N bond in the metal complexes with Schiff base ligand comprising an additional nitrogen atom from a heterocycle (i.e. compounds **I-IV**) are more stable under physiological conditions.

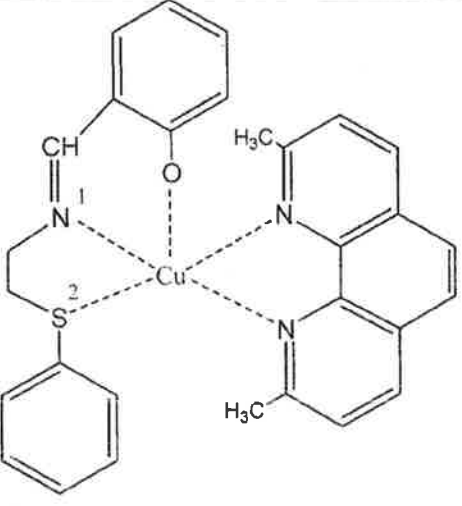
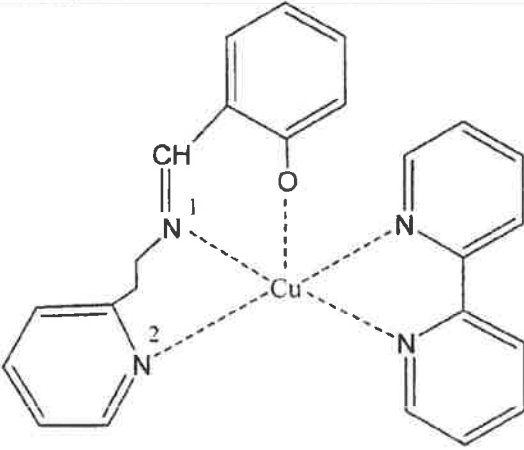
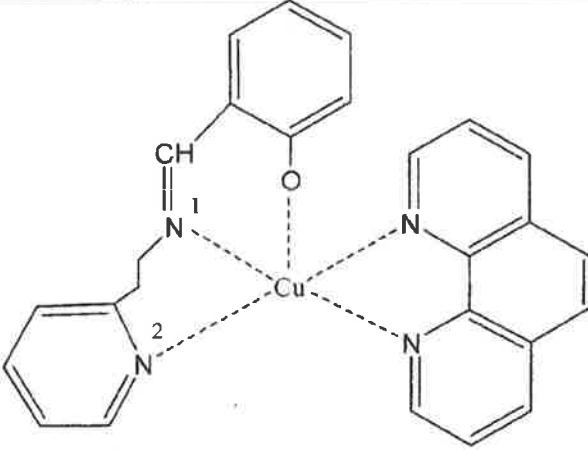
Crystal structures of some of the complexes listed in Table 8 have been determined. The bond length data suggests that Cu-N bond in the metal complex with Schiff base ligand comprising an additional nitrogen atom from a

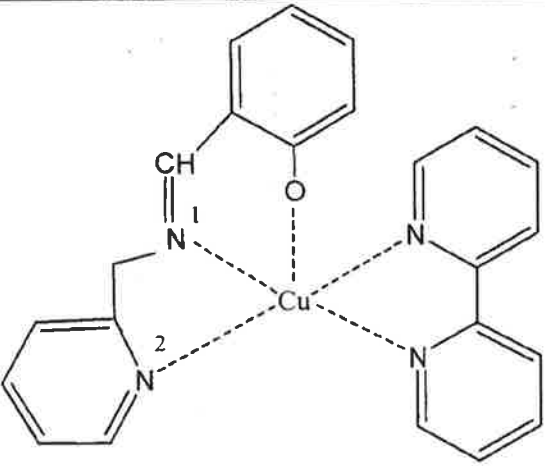
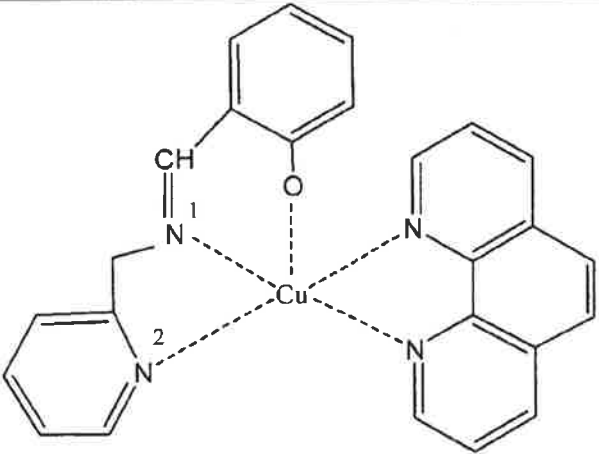
heterocycle is stronger than Cu-S bond in sulphur containing Schiff base metal ligand complexes. This also demonstrates the greater stability of the metal complexes with a Schiff base ligand comprising an additional
5 nitrogen atom from a heterocycle over sulphur-containing Schiff base metal ligand complexes.

Table 8.

Compound Structure	Bond distances (Å)	Imine C=N IR frequency (cm^{-1})
(a) 	Cu - S 2.7649 Cu - N¹ 1.949	1612 [Ref 1]
(b) 	Cu - S 2.7887 Cu - N¹ 1.941	1612 [Ref 1]

 (c)	Cu - S 2.3523 Cu - N ¹ 1.967	1612 [Ref 1]
 (d)	Not determine d	1605 [Ref 2]
	Crystal structure reported, data not accessibl e	1614 [Ref 2]

 (e)		
 (I)	Not determine d	1626
 (II)	Not determine d	1625

 (III)	Not determine d	1631
 (IV)	Cu-N ¹ 2.033 Cu-N ² 1.940	1633

Ref 1 - *Journal of Inorganic Biochemistry*, **2004**, 98, 377 - 386
 Ref 2 - *J. Am. Chem. Soc.* **2003**, 125, 12118 - 12124

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Applications

The compounds disclosed herein provide a novel compound for use in photodynamic therapy.

Advantageously, the compounds can be produced at a high purity and has improved aqueous solubility.

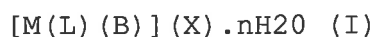
Advantageously, the compounds are photochemically active in the wavelength 390 - 750 nm, and especially in the region of 600 to 700 nm where tissue penetration is effective.

Advantageously, a metal complex with a Schiff base ligand comprising an additional nitrogen atom from a heterocycle is stable *in vivo*, particularly relative to known Schiff base metal ligand complexes that do not contain additional nitrogen, such as sulphur-containing Schiff base metal ligand complexes.

It will be apparent that various other modifications and adaptations of the invention will be apparent to the person skilled in the art after reading the foregoing disclosure without departing from the spirit and scope of the invention and it is intended that all such modifications and adaptations come within the scope of the appended claims.

Claims

1. A metal-ligand complex comprising a transition metal complexed with at least one nitrogen-containing Schiff base ligand and at least one nucleic acid intercalating moiety, of the formula (I):



wherein, M is a transition metal;

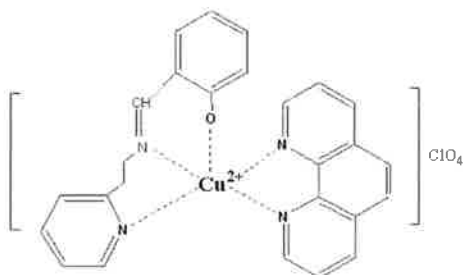
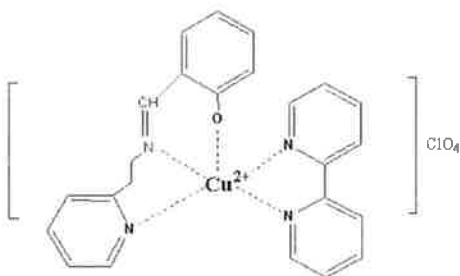
L is a nitrogen-containing heterocyclic Schiff base ligand,

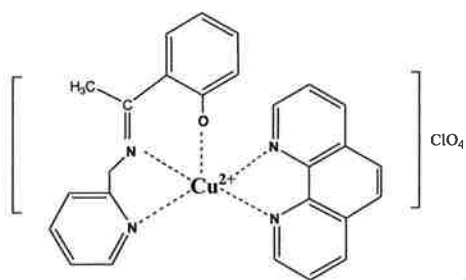
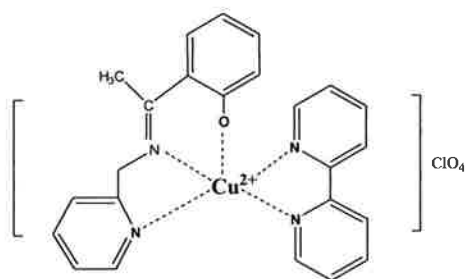
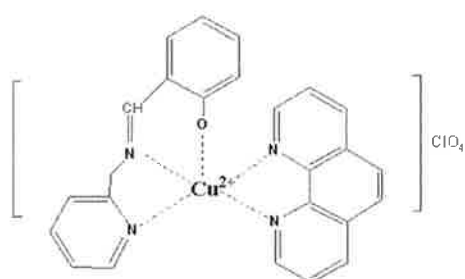
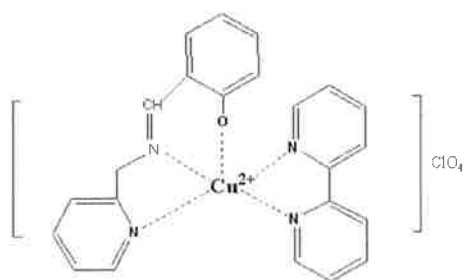
B is a nucleic acid intercalating moiety,

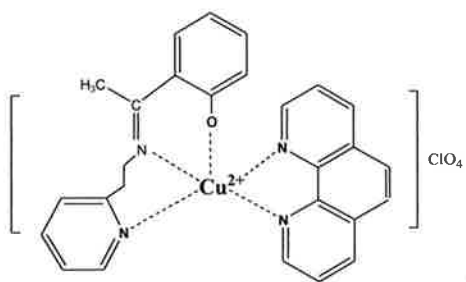
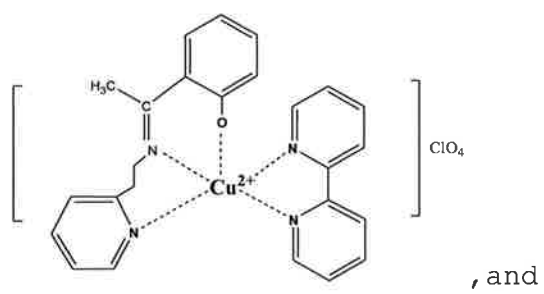
X is an anion, and

n is selected from 0 to 5,

wherein said metal-ligand complex is selected from the group consisting of







2. The complex as claimed in claim 1, wherein said compound is photosensitive to light of a wavelength from 10-1000nm.
3. The complex as claimed in claim 2, wherein said light is of a wavelength from 10-400nm.
4. The complex as claimed in claim 2, wherein said light is of a wavelength from 390-750nm.
5. The complex as claimed in claim 2, wherein said light is of a wavelength from 700-800nm.
6. A pharmaceutical composition comprising a complex as claimed in any one of claims 1 to 5, in admixture with a pharmaceutically acceptable carrier.
7. Use of a complex as claimed in any one of claims 1 to 5 or a composition as claimed in claim 6 in the manufacture of a medicament for the treatment of cancer.
8. The use as claimed in claim 7, wherein the cancer is selected from the group consisting of skin cancer, lung cancer, stomach cancer, prostate cancer and pancreatic cancer.
9. The use as claimed in claim 8, wherein the skin cancer is selected from squamous cell carcinoma, basal cell carcinoma and melanoma.
10. The use as claimed in claim 8, wherein the lung cancer is non-small cell lung cancer or small cell lung cancer.

11. Use of a complex as claimed in any one of claims 1 to 5 or a composition as claimed in claim 6 in the manufacture of a medicament for the treatment of a precancer.

12. The use as claimed in claim 11, wherein the precancer is selected from Bowen's disease (squamous cell carcinoma in situ) or Barrett's oesophagus.

13. Use of a complex as claimed in any one of claims 1 to 5 or a composition as claimed in claim 6 in the manufacture of a medicament for the treatment of macular degeneration.

14. Use of a complex as claimed in any one of claims 1 to 5 or a composition as claimed in claim 6 in the manufacture of a medicament for the treatment of human papilloma virus (HPV) warts.

15. Use of a complex as claimed in any one of claims 1 to 5 or a composition as claimed in claim 6 in the manufacture of a medicament for the treatment of a skin disorder.

16. A kit comprising a complex as claimed in any one of claims 1 to 5 or a composition as claimed in claim 6, together with instructions for use.

17. The kit as claimed in claim 16, wherein the kit contains one or more further therapeutic agents.