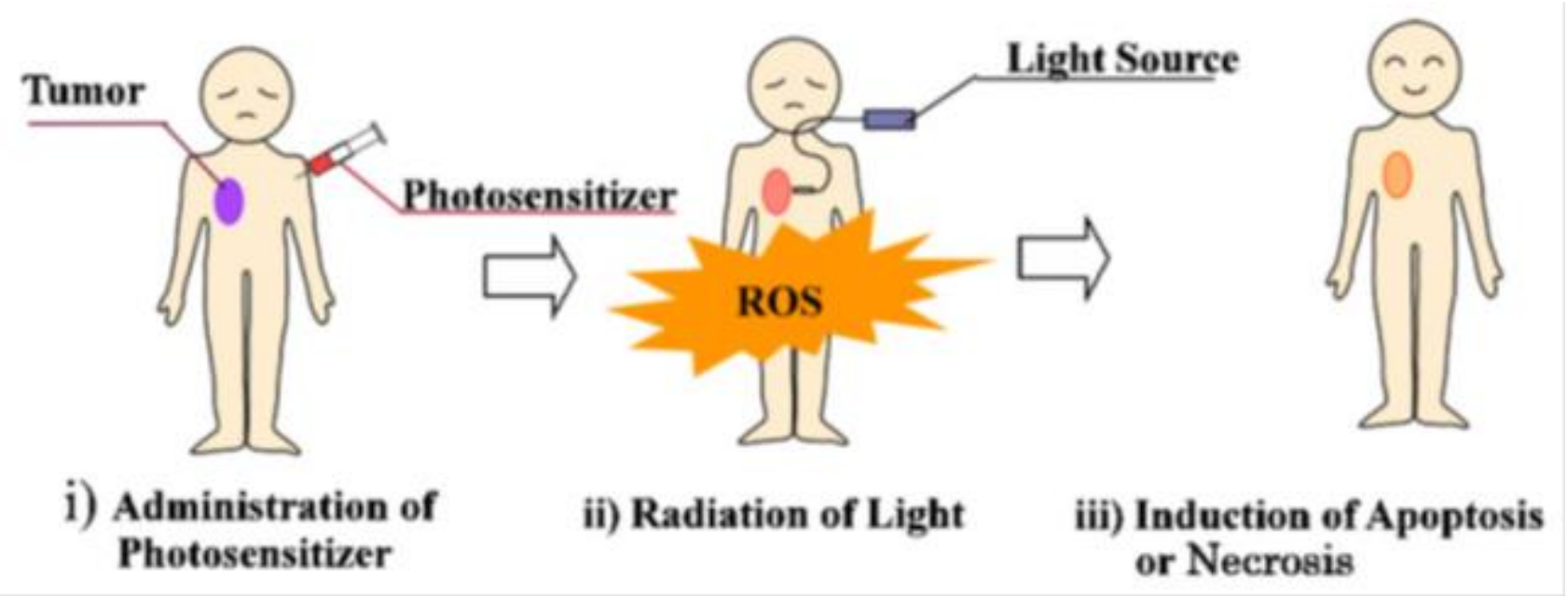
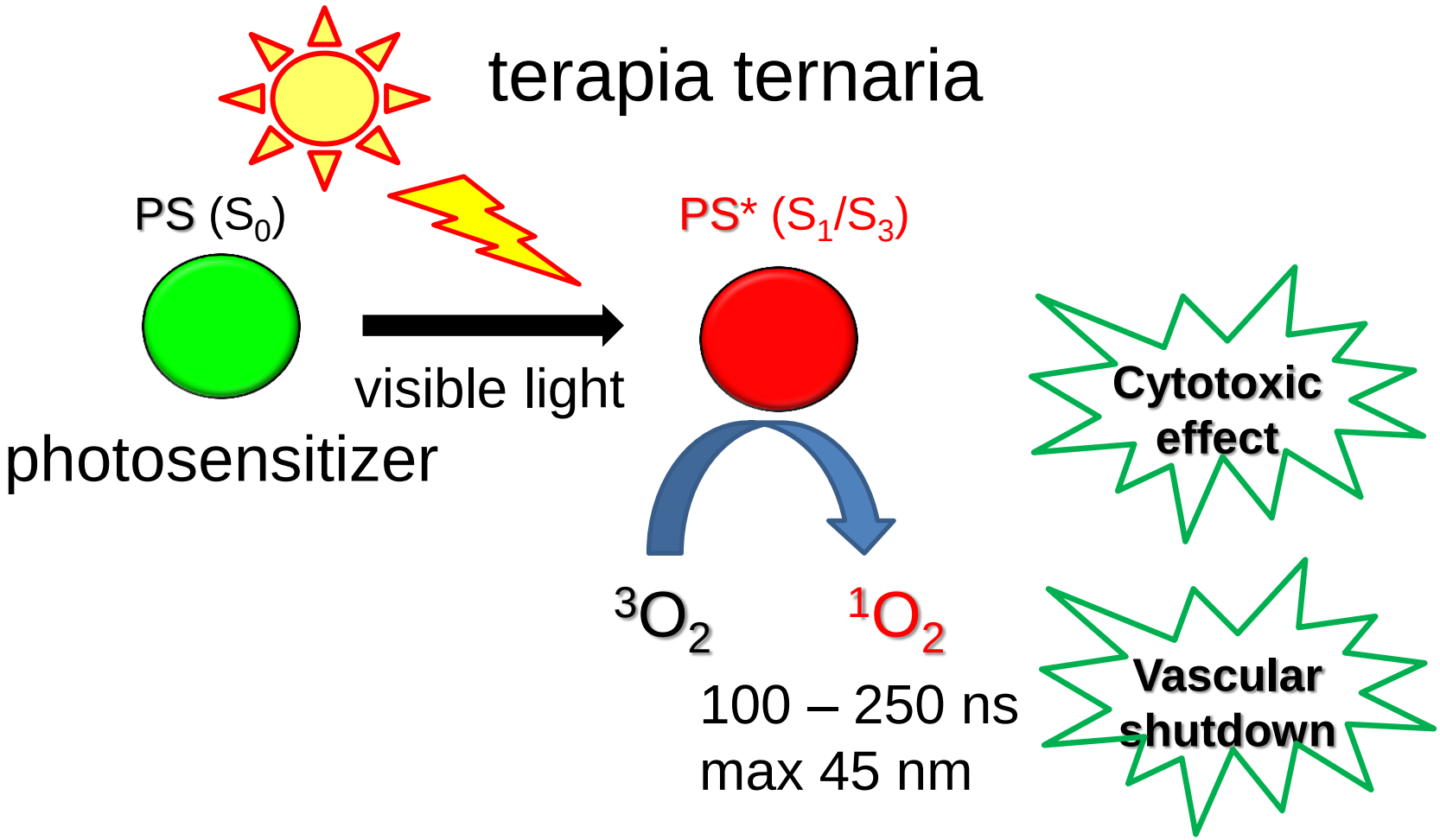
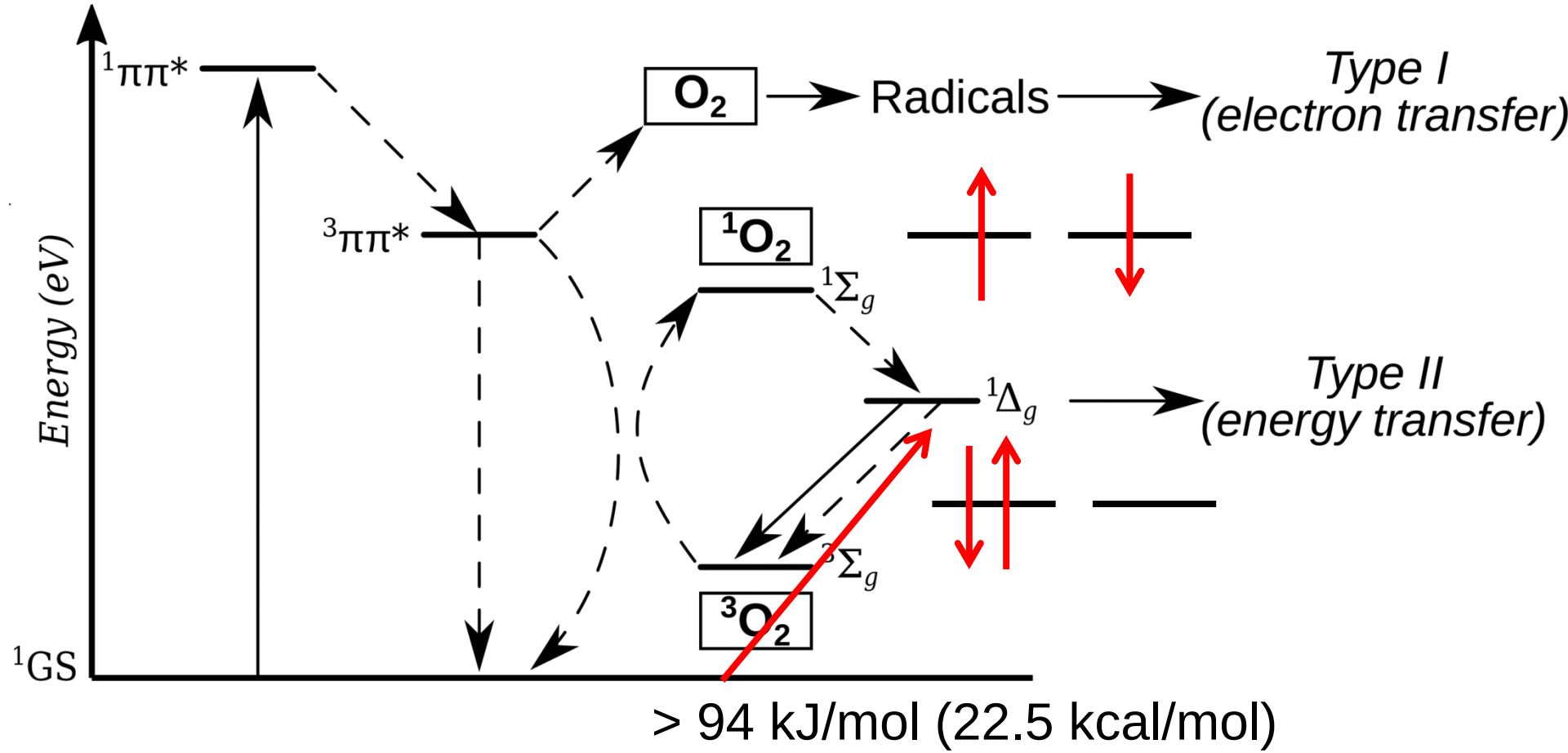
Terapia Fotodinamica (PDT)

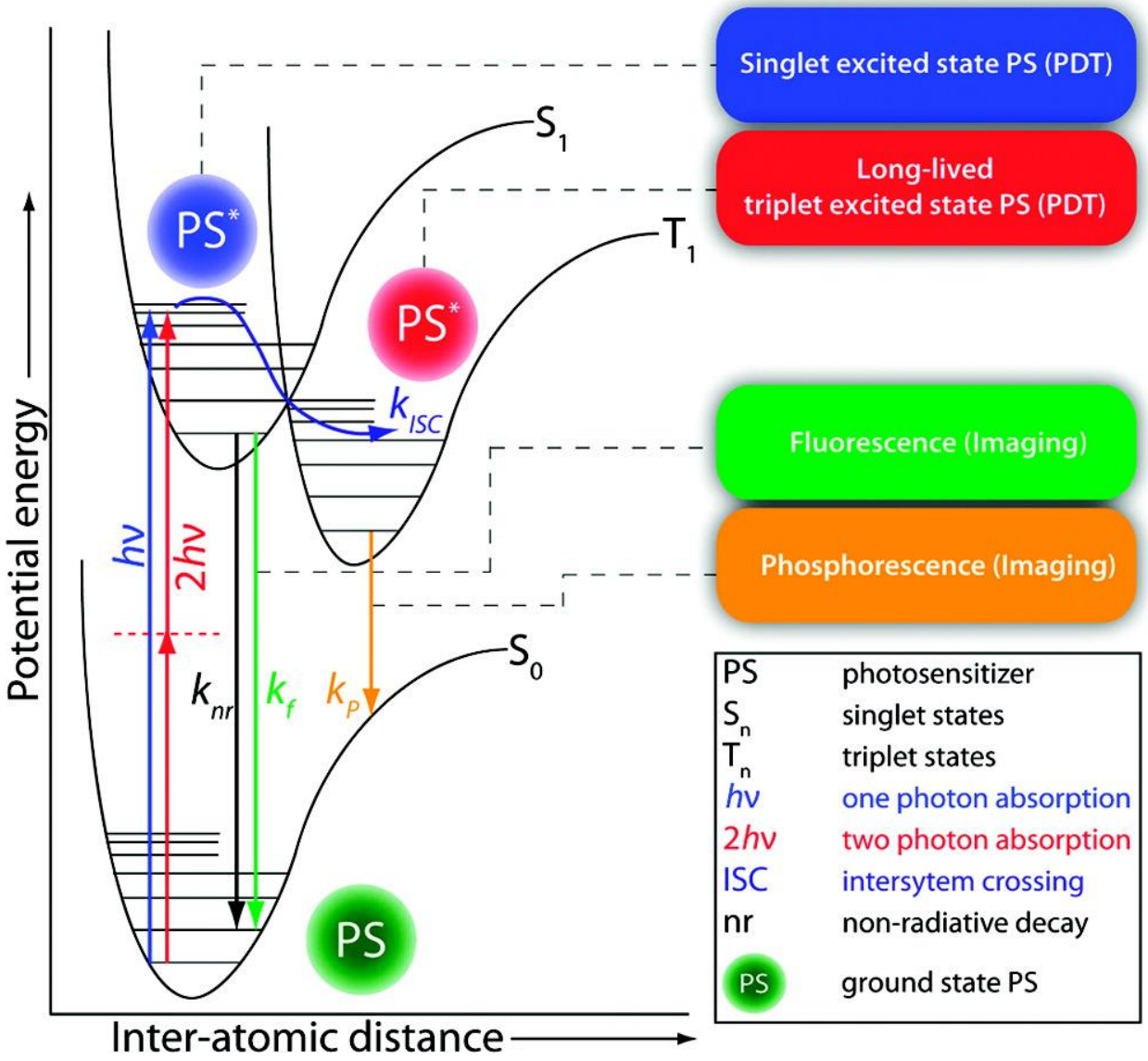


Controllo spazio-temporale

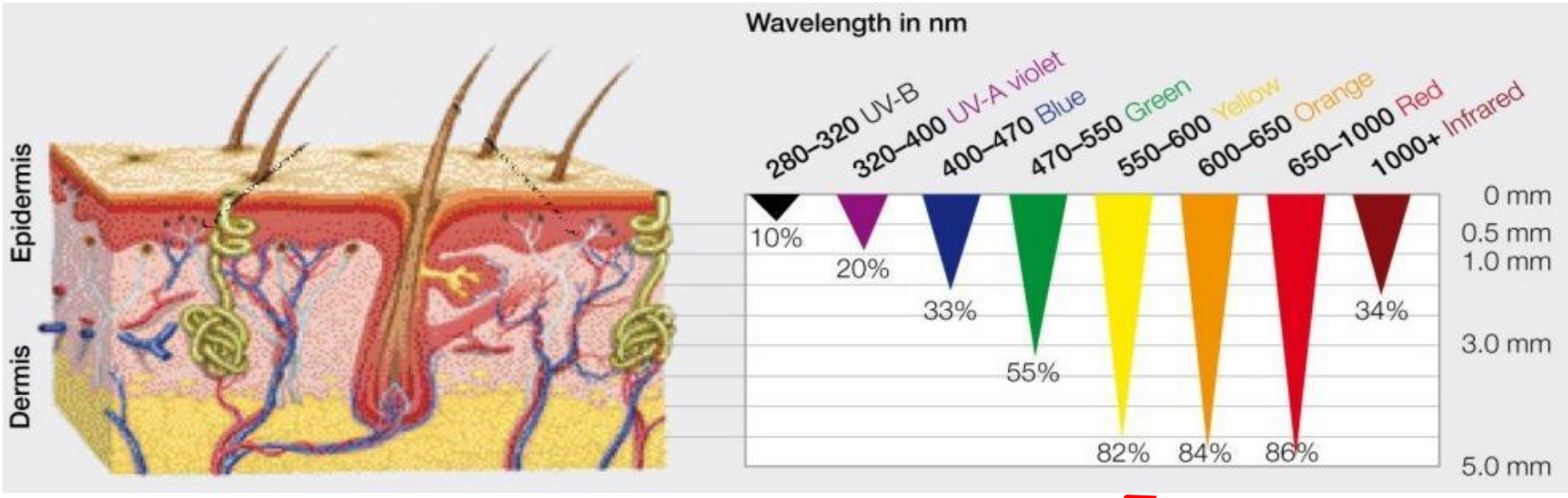
Terapia Fotodinamica (PDT)




Energy (eV)
$^1\pi\pi^*$
$^3\pi\pi^*$
^1GS
O_2
Radicals
Type I
(electron transfer)
$^1O_2$
$^1\Sigma_g$
$^1\Delta_g$
Type II
(energy transfer)
$^3\Sigma_g$
$^3O_2$
> 94 kJ/mol (22.5 kcal/mol)


Singlet excited state PS (PDT)
Long-lived
triplet excited state PS (PDT)
Fluorescence (Imaging)
Phosphorescence (Imaging)
Potential energy
Inter-atomic distance
S1
T1
S0
PS*
PS*
PS
kISC
hν
2hν
knr
kf
kP
PS photosensitizer
Sn singlet states
Tn triplet states
hν one photon absorption
2hν two photon absorption
ISC intersytem crossing
nr non-radiative decay
PS ground state PS

Tissue penetration of light



PDT window

ΔE between $^1O_2$ and $^3O_2$ = 94 kJ/mol

This energy gap is compatible with photosensitizers that have absorption maxima up to over 800 nm (their triplet excited state is still higher in energy than the ground state of $^3O_2$.

The ideal photosensitizer

- Absorbs strongly in the PDT window (600 – 900 nm)
- Has a high $^1O_2$ quantum yield
- Is photostable (no photo-bleaching)
- Is non-toxic in the dark
- Localizes selectively in the diseased tissue
- Has a rapid clearance

Macrocicli tetrapirrolici come PS

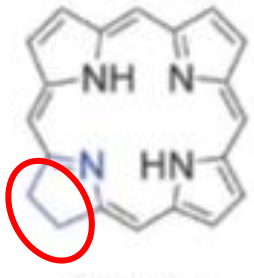
22π 600 – 650nm

18π 700 – 800nm

20π 630 – 700nm

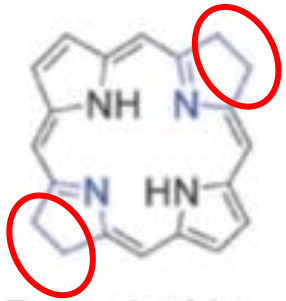
Porphyrin

a



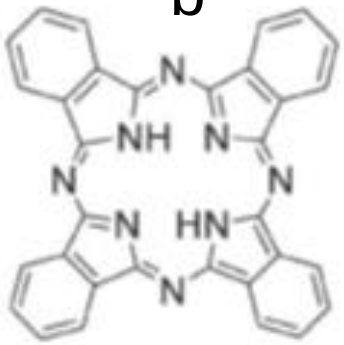
Chlorin

b



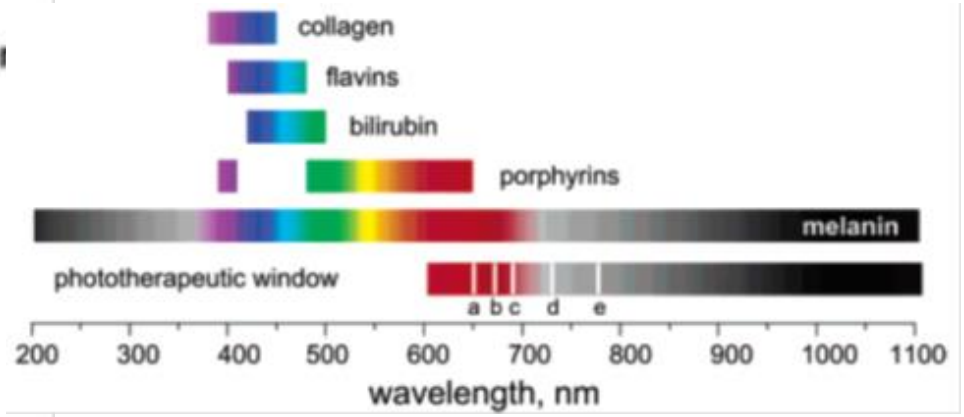
Bacteriochlor

c



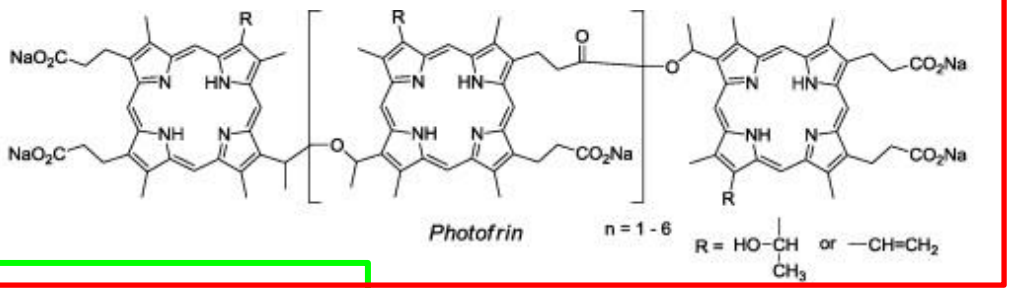
Phthalocyanine

d

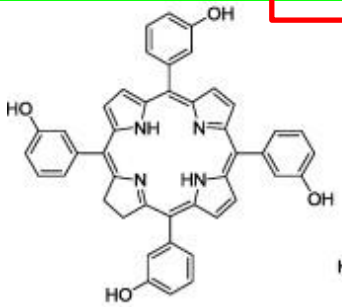


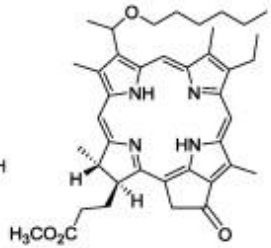
Fotosensibilizzatori per PDT di prima e seconda generazione

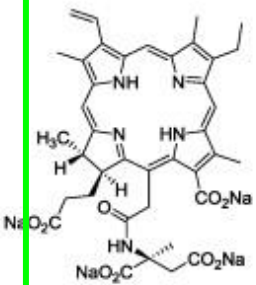
λ = 652
ε = 3×10^4 $M^{-1}cm^{-1}$

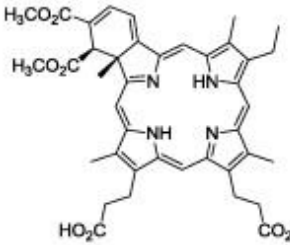


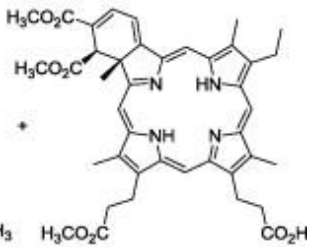
λ = 630
ε = 1170 $M^{-1}cm^{-1}$

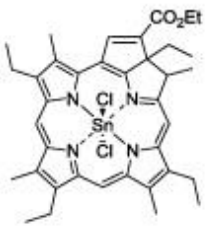

Foscan

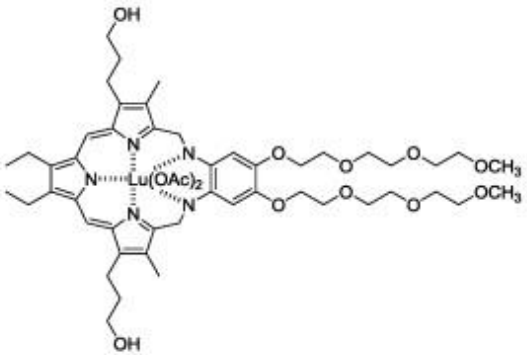

Photochlor

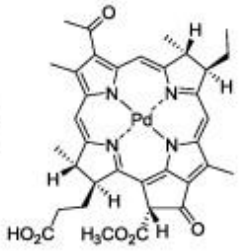

Talaporfin sodium

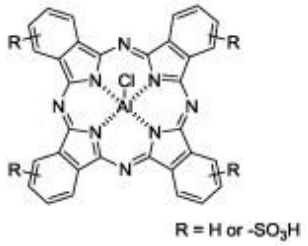

Visudyne




Purlytin

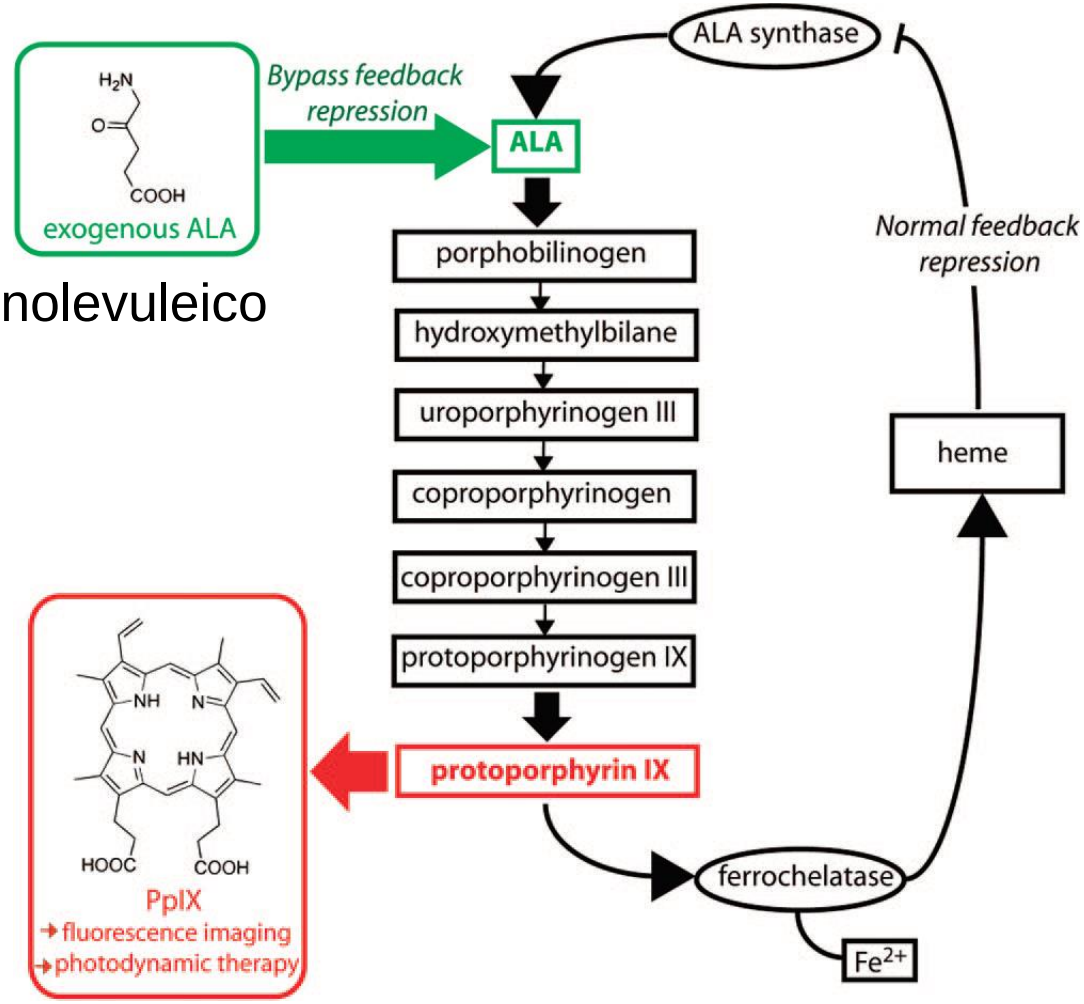

Lutrin

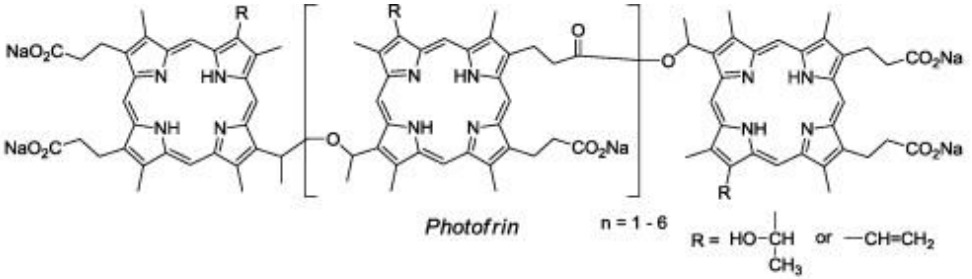

Tookad

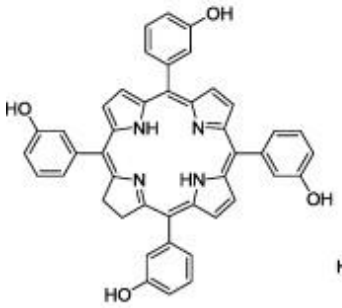

R = H or -SO_3H
Photosens

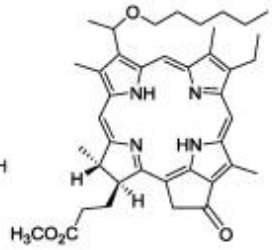
Tumori della pelle non-pigmentati: ALA-PDT

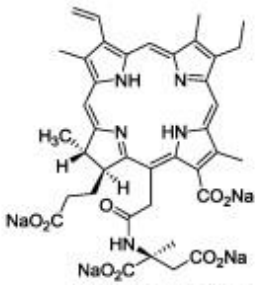
acido 5-aminolevuleico

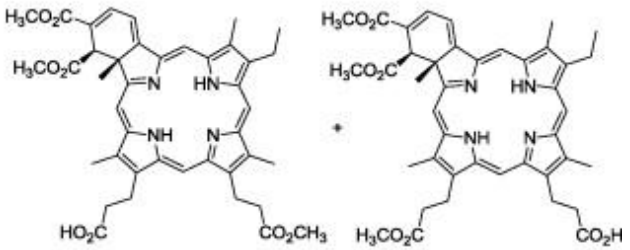


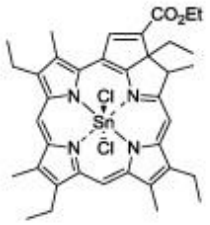


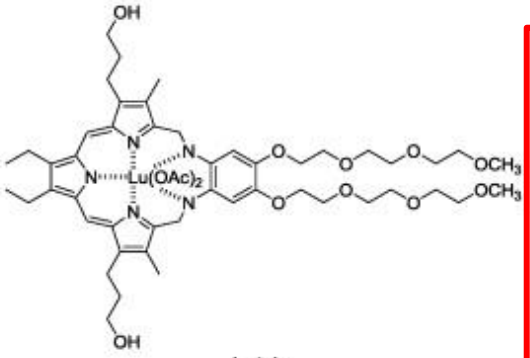

Foscan

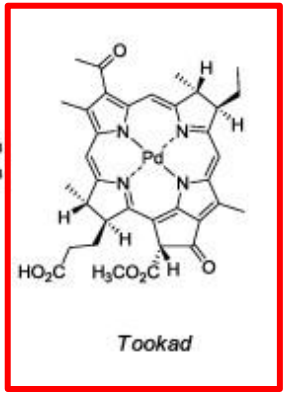

Photochlor

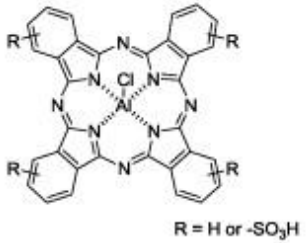

Talaporfin sodium


Visudyne

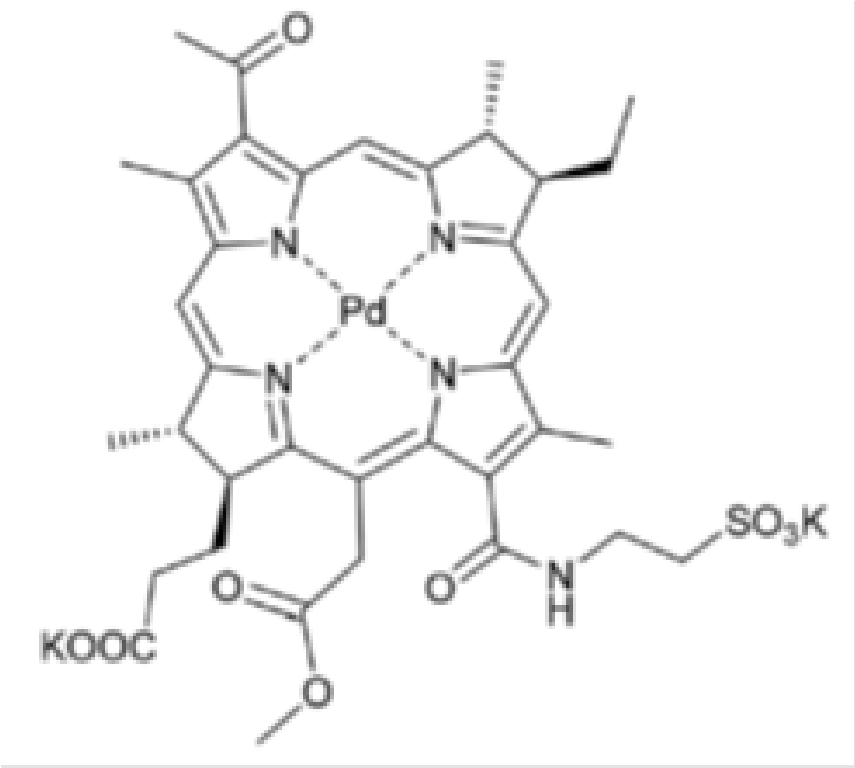

Purlytin


Lutrin


Tookad



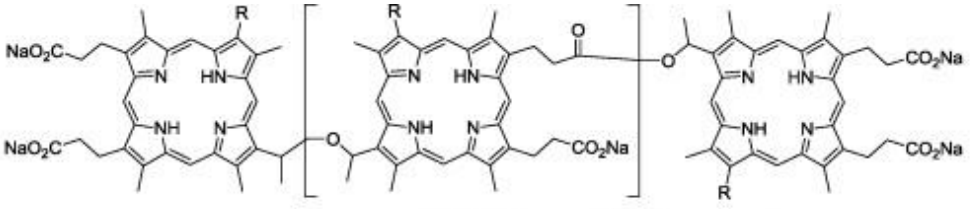
Photosens

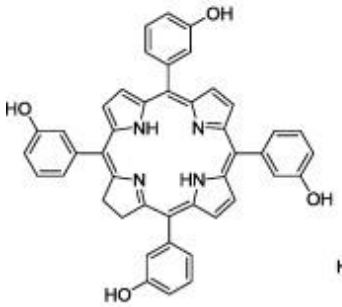


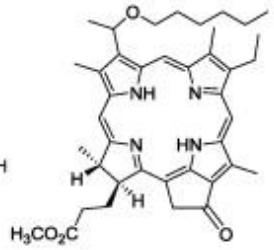
TOOKAD-solubile

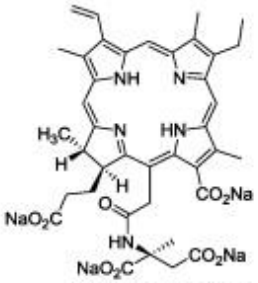
(palladio-batteriofeoforbide)

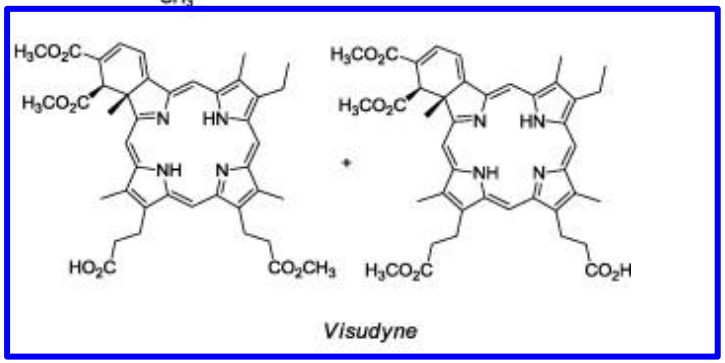
azione prevalente a livello vascolare



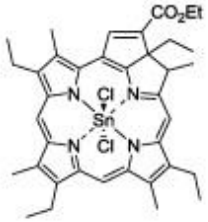

Foscan

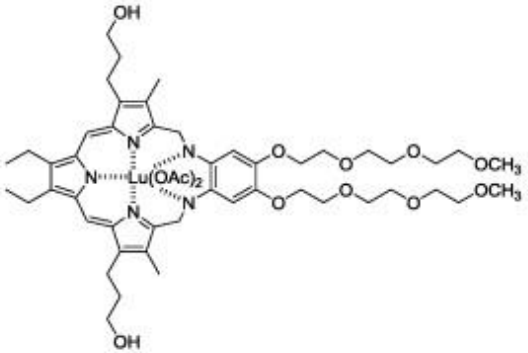

Photochlor

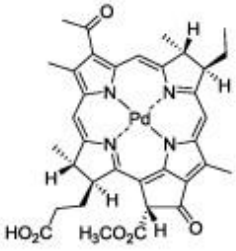

Talaporfin sodium

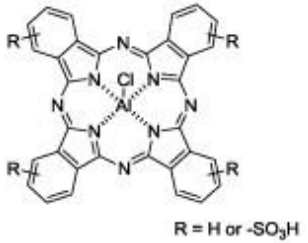

Visudyne

degenerazione maculare senile
First line treatment


Purlytin

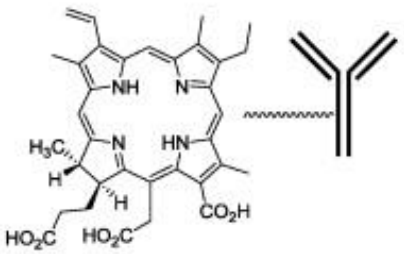

Lutrin


Tookad

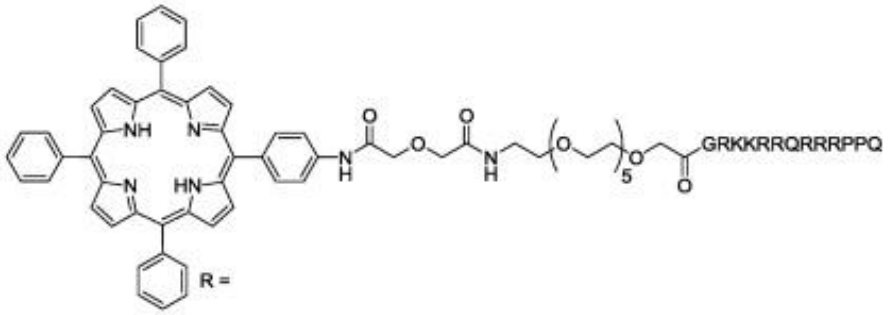


Photosens

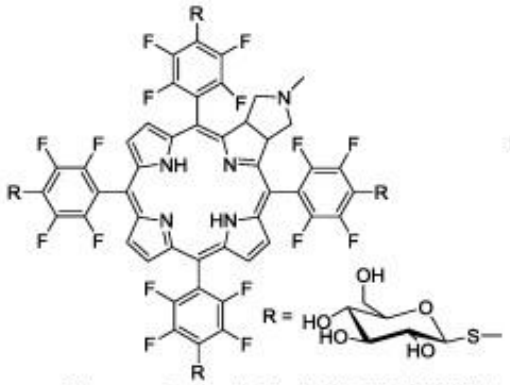
Fotosensibilizzatori per PDT di terza generazione (*targeted*)



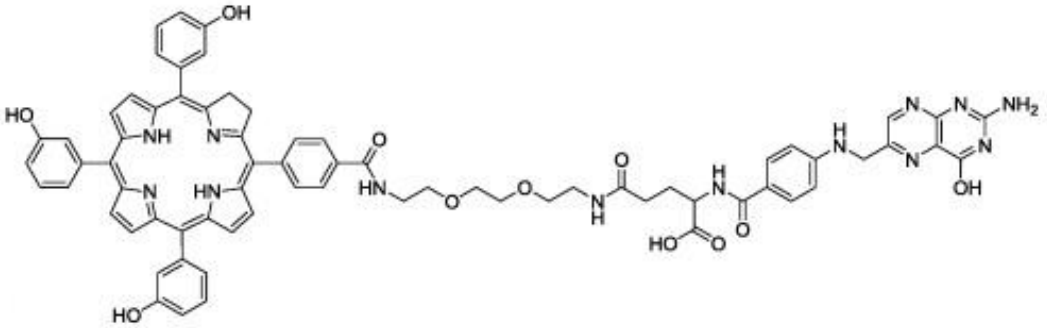
IgG conjugated chlorin



HIV-1 Tat peptide conjugated porphyrin

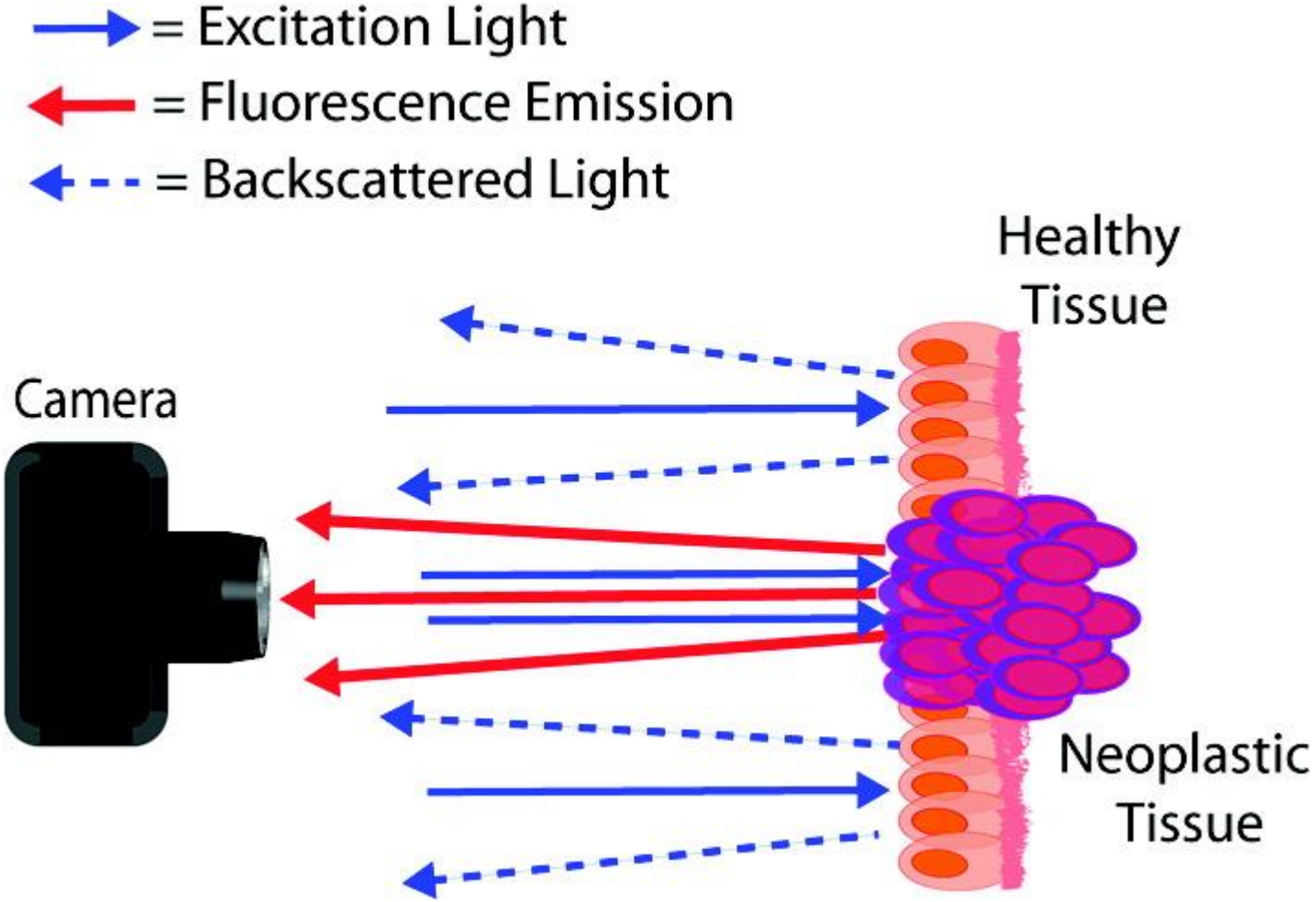


Glycoconjugated chlorin (H_2TFPC-SGlc)

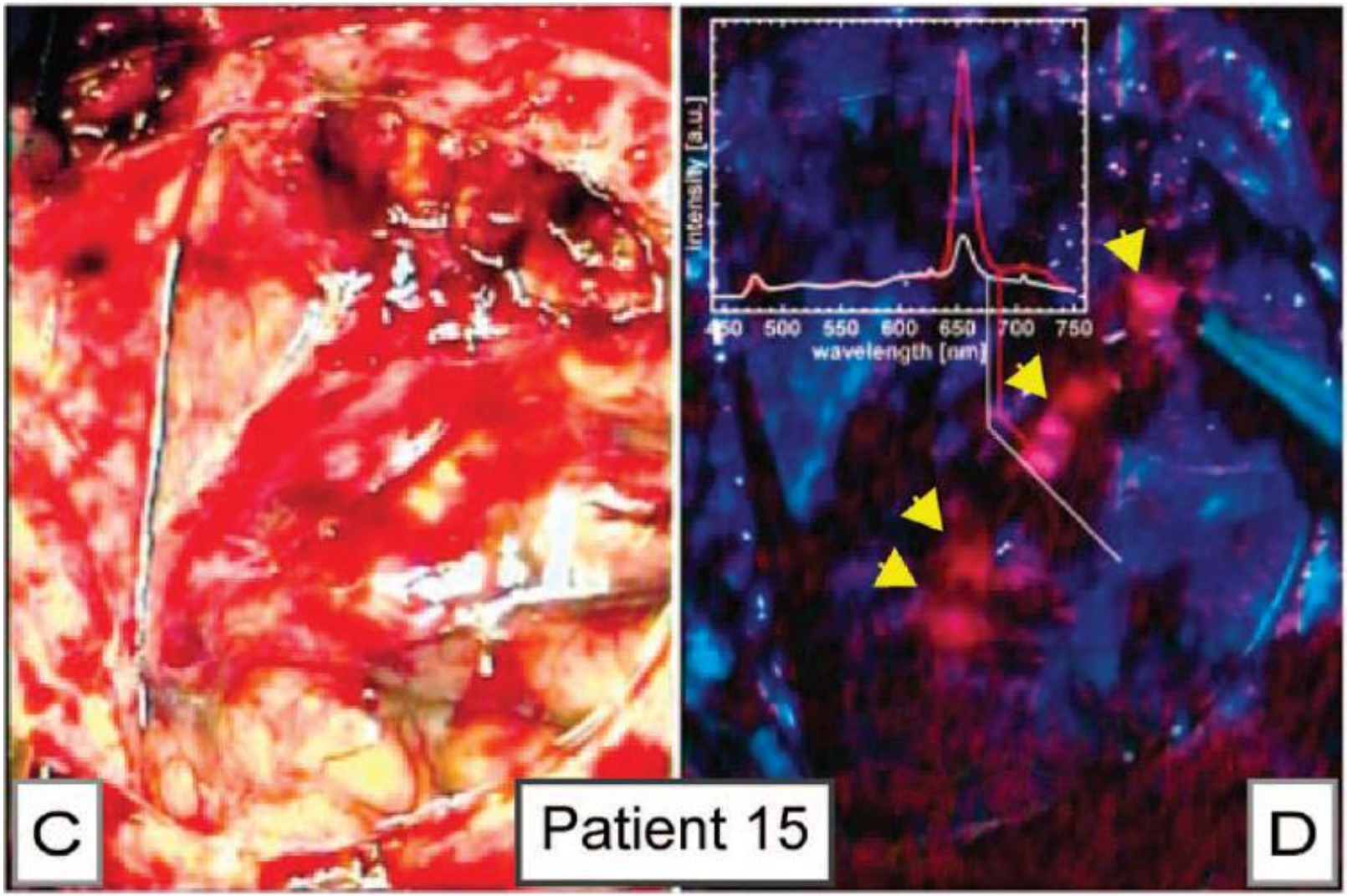


Folate conjugated temoporfin

Tumor margin resection with *tumor avid* PS's

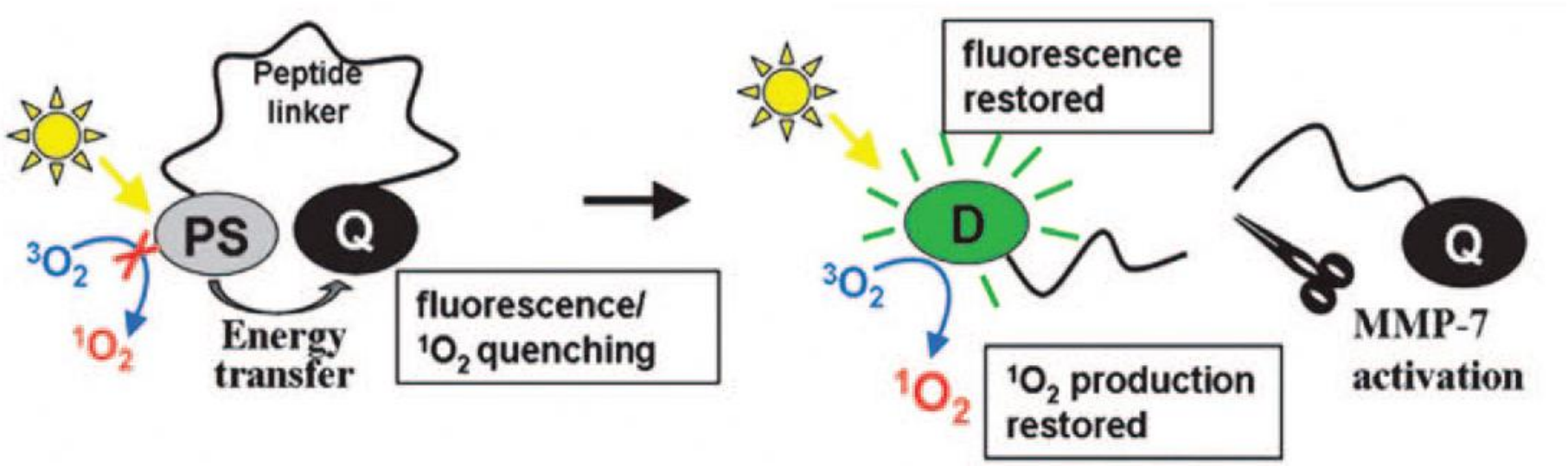


Brain tumor, patient treated with Foscan

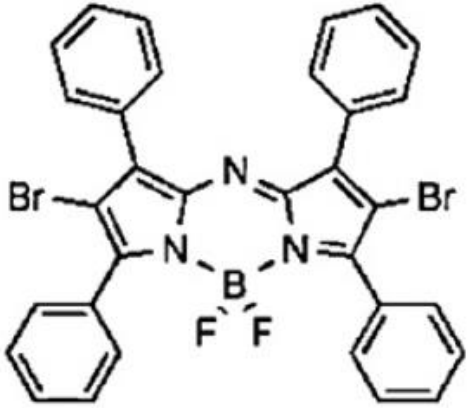


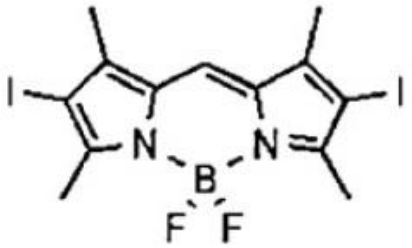
Blue light

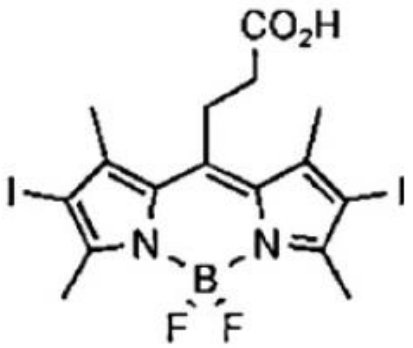
Site-activated constructs



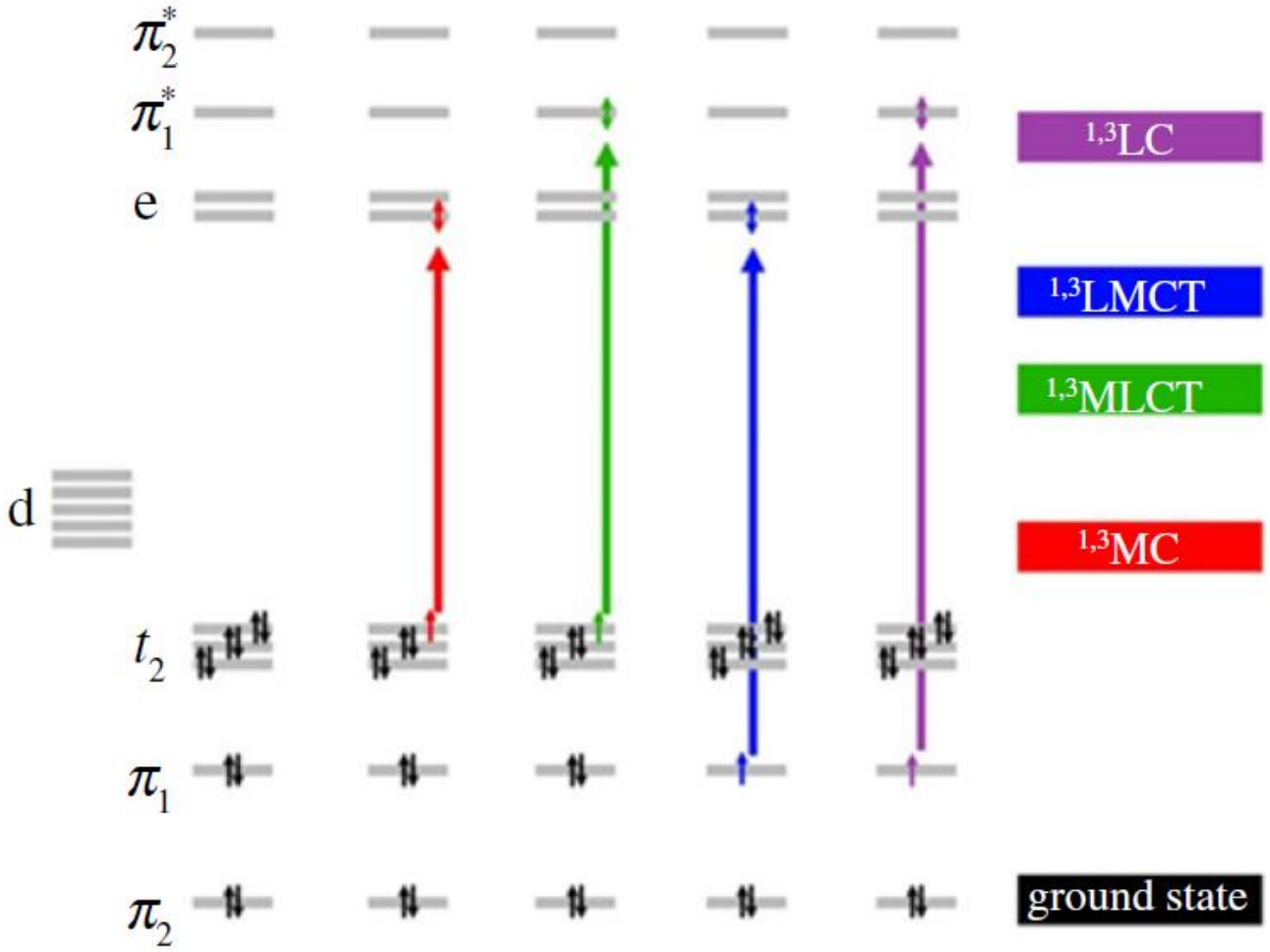
Derivati del BODIPY (*boron-dipyrromethene)*



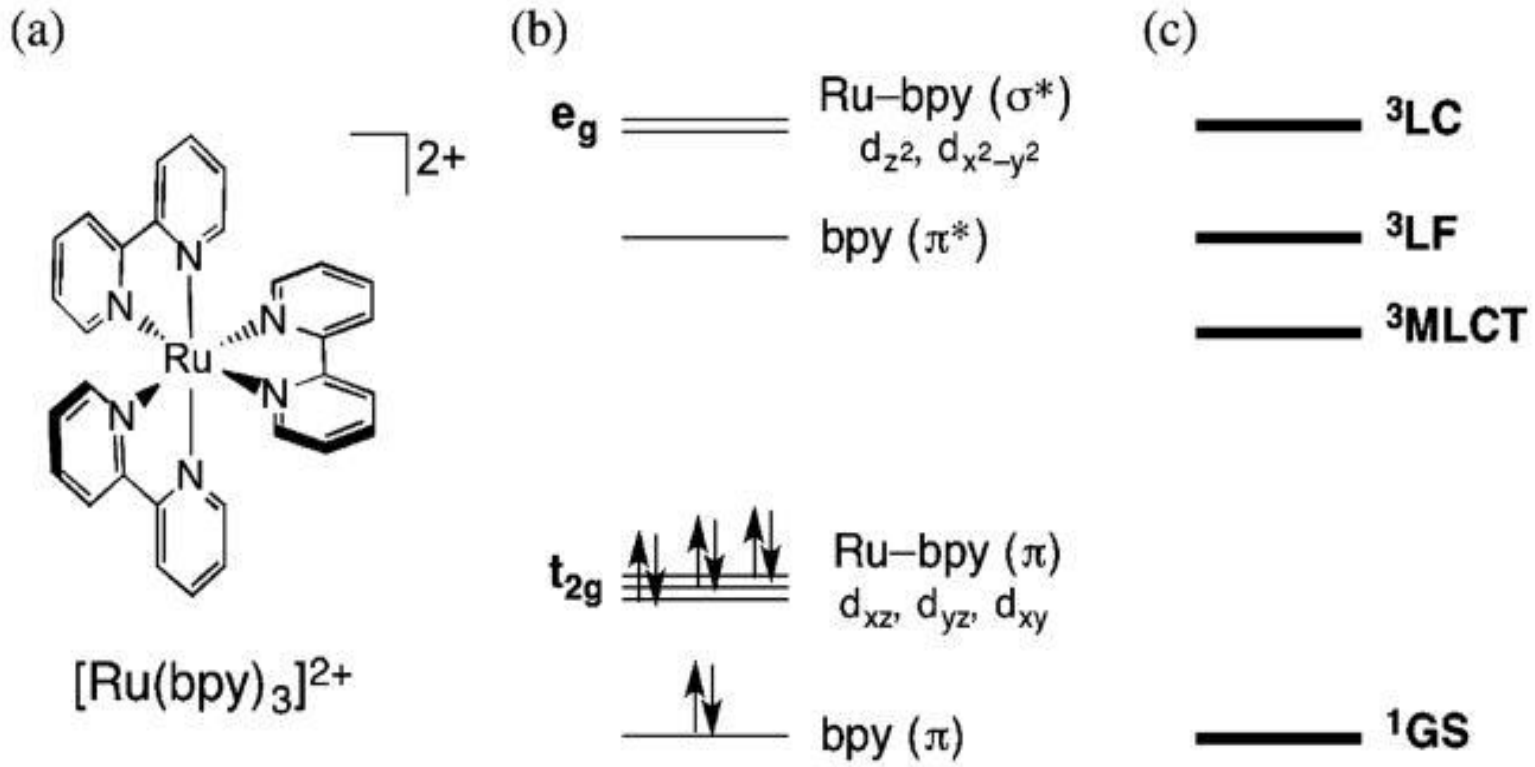




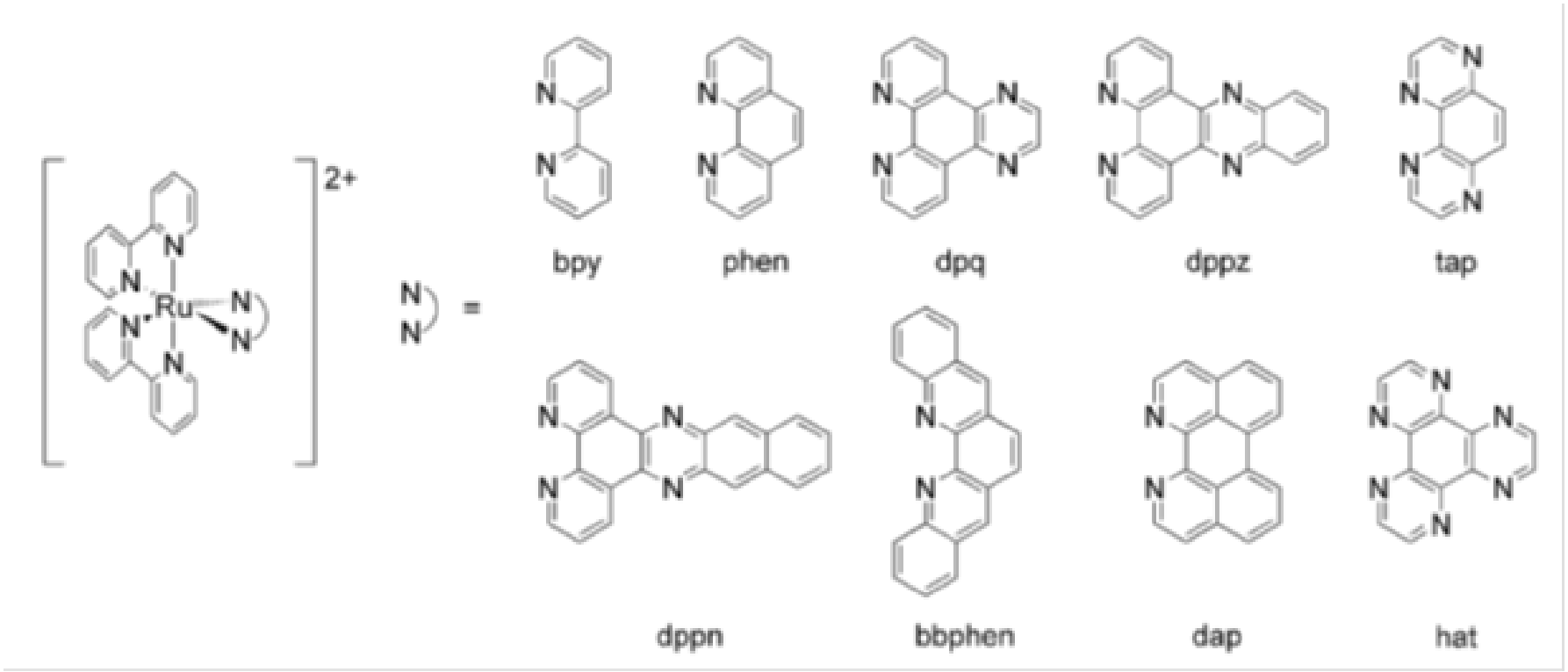
Photoactivatable metal compounds



Diagrammi semplificati degli MO di frontiera e degli stati di $[Ru(bpy)_3]^{2+}$

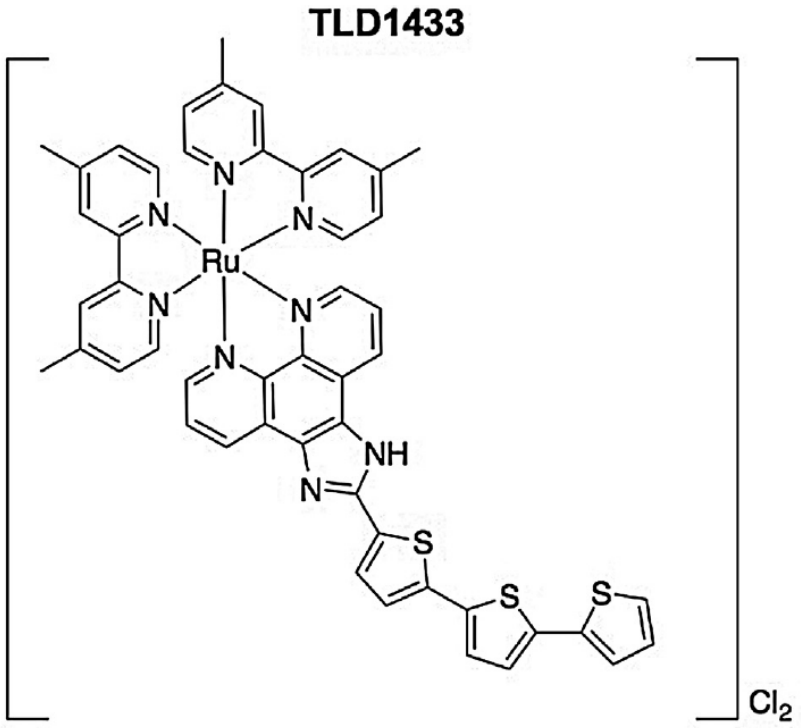


Metal compounds for PDT

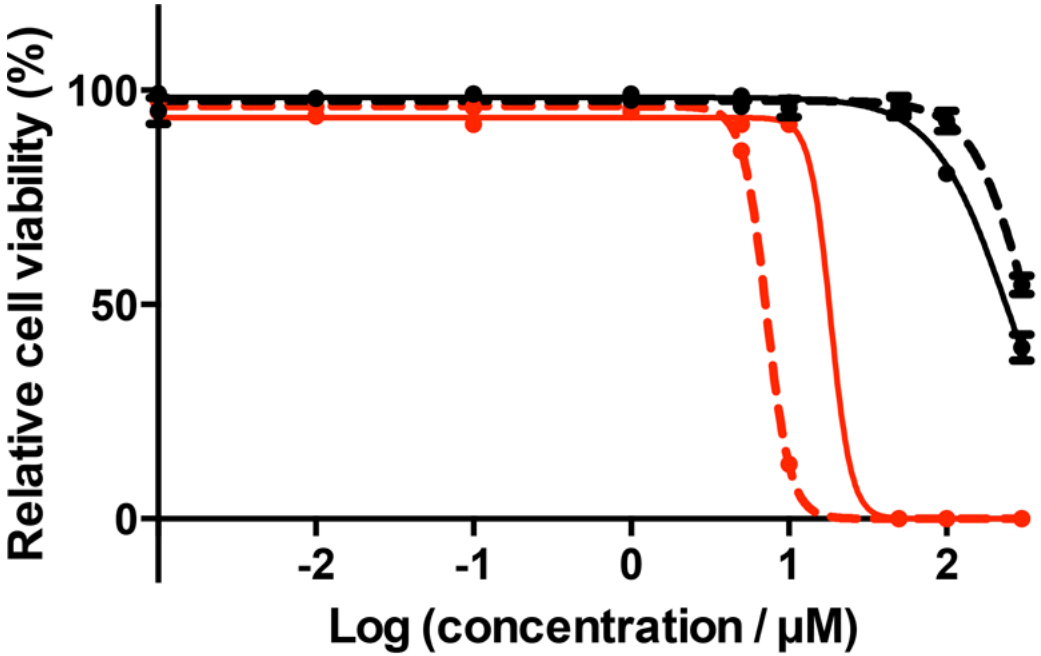


Health Canada Approves Clinical Trial Application for Anti-Cancer Drug

Toronto, Ontario – December 17, 2015, Theralase Technologies Inc. ("Theralase" or the "Company") (TLT:TSXV) (TLTFF:OTC), a leading biotechnology manufacturer focused on commercializing medical technologies to eliminate pain and destroy cancer, announced today that Health Canada has approved its next generation anti-cancer drug, TLD-1433, under Clinical Trial Application ("CTA") for evaluation in a Phase Ib clinical trial for patients inflicted with Non-Muscle Invasive Bladder Cancer ("NMIBC").



In vitro studies

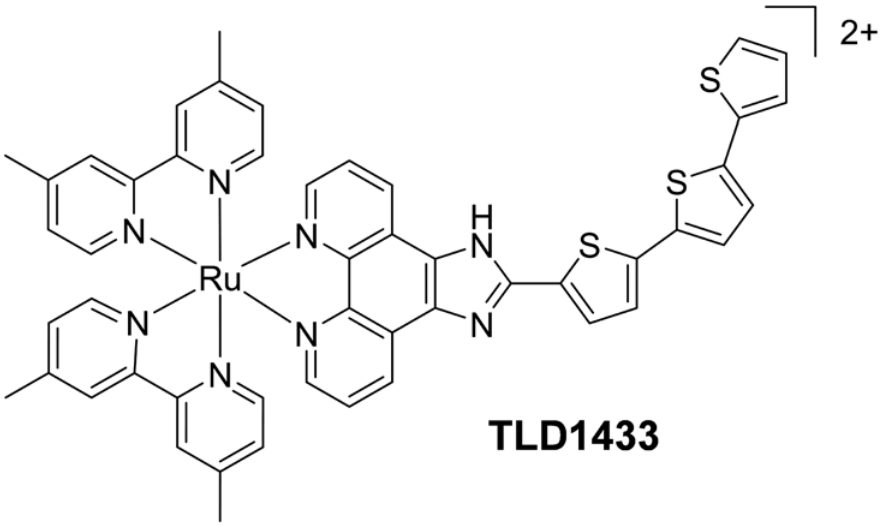


TLD1433, Dark EC_{50} > 300 µM

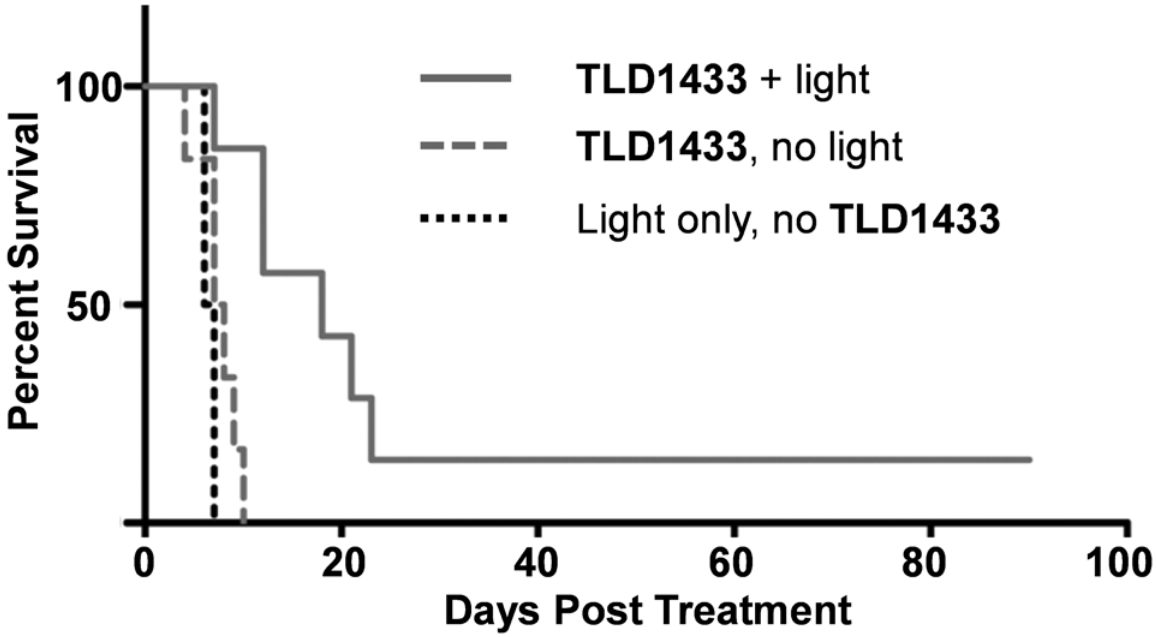
TLD1433, Red EC_{50} = 7.20 ± 1.10 µM

$[Os(dmb)_2(IP\text{-}3T)]Cl_2$, Dark EC_{50} = 242 ± 3 µM

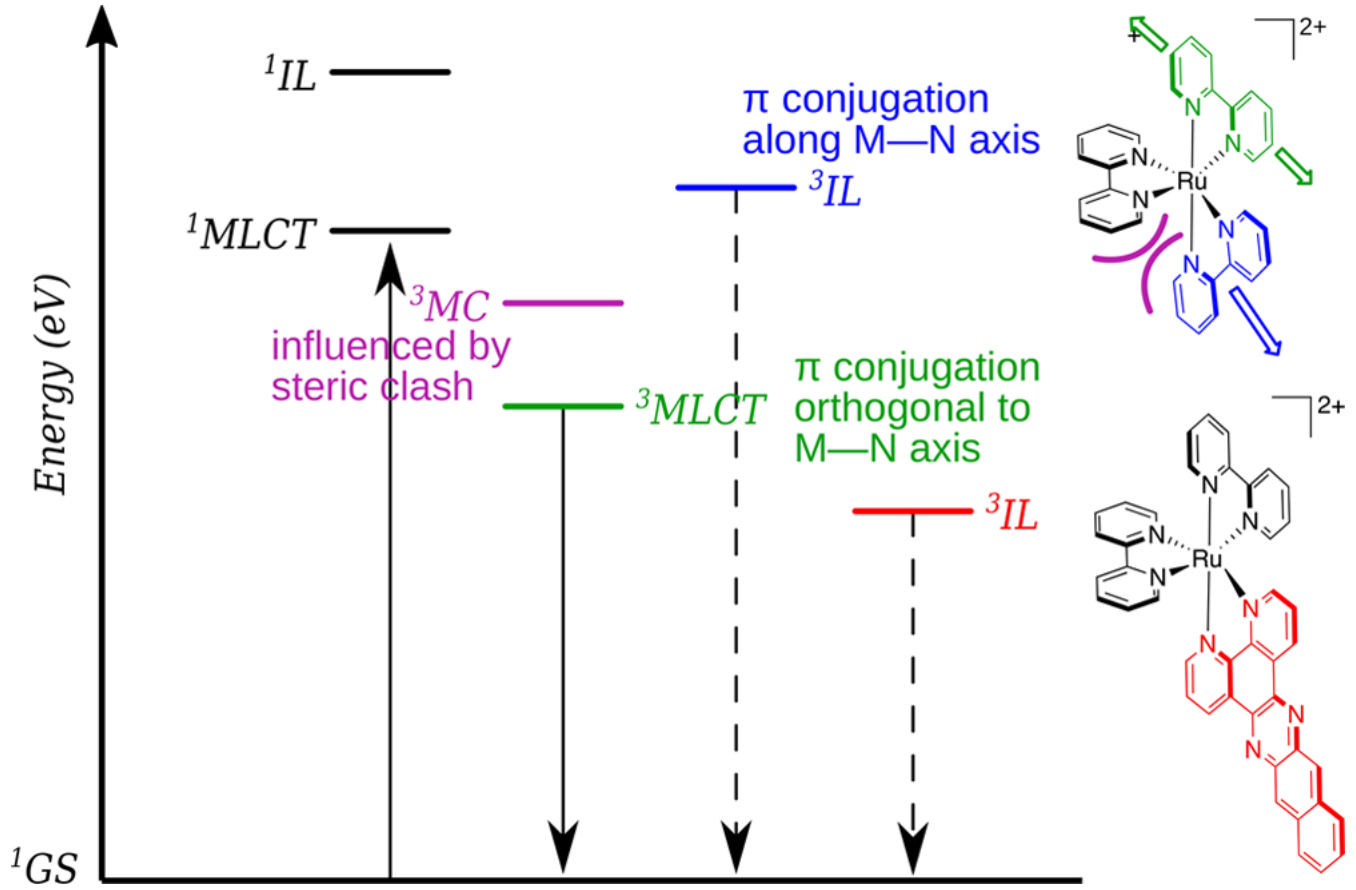
$[Os(dmb)_2(IP\text{-}3T)]Cl_2$, Red EC_{50} = 18.4 ± 0.1 µM


2+
S
S
S
H
N
N
N
N
N
N
N
N
Ru

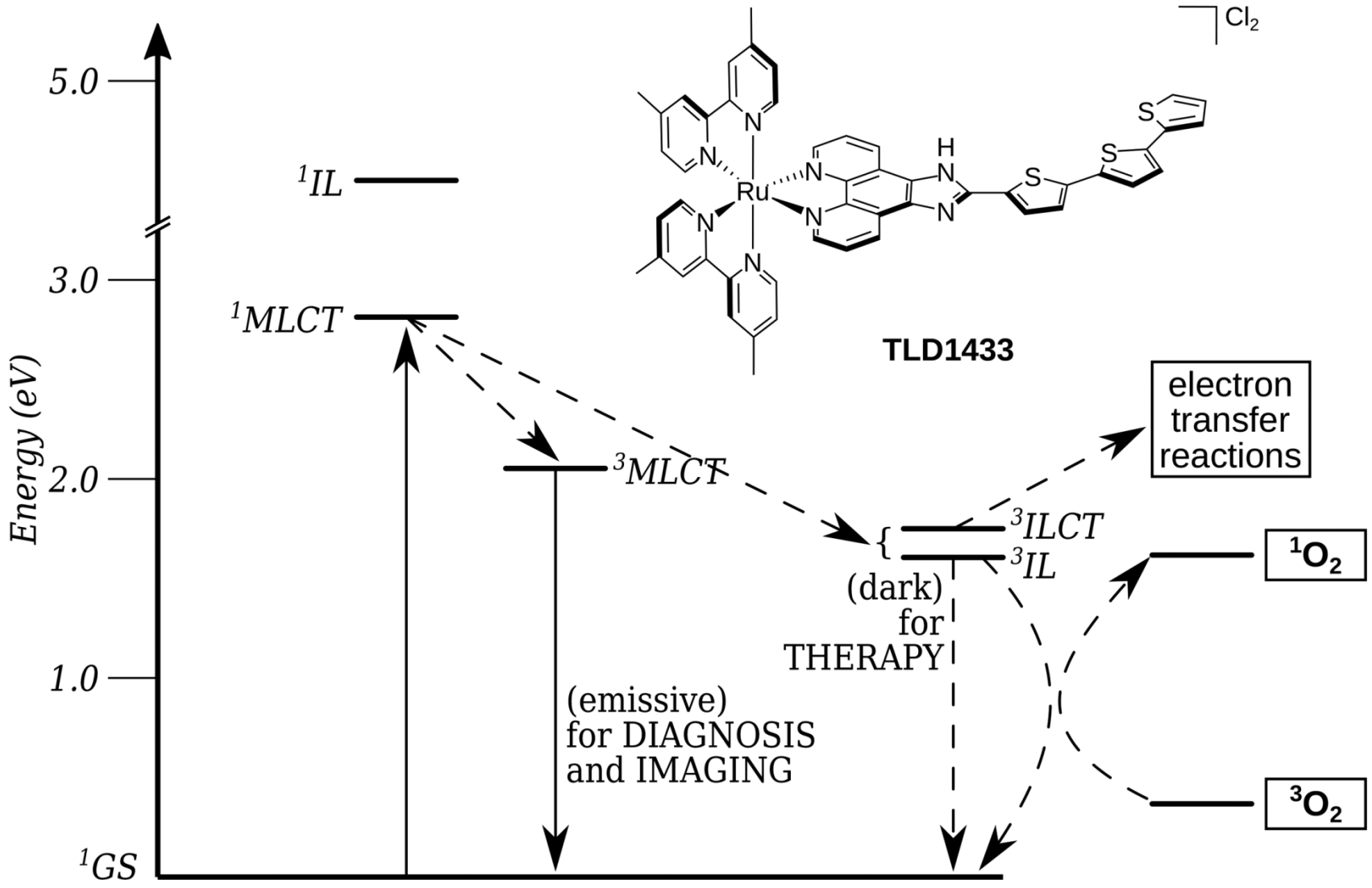
TLD1433


100
50
Percent Survival
0
20
40
60
80
100
Days Post Treatment
TLD1433 + light
TLD1433, no light
Light only, no TLD1433

Elementi di design molecolare



Aumentare la coniugazione π di un legante diiminico fa diminuire l'energia dello stato eccitato ^{3}IL (*intraligand*), con conseguente aumento del suo tempo di vita e maggior produzione di $^1O_2$.


5.0
3.0
2.0
1.0
Energy (eV)
^1IL
^1MLCT
^3MLCT
^3ILCT
^3IL
^1GS
Cl2
Ru
N
H
S
TLD1433
electron transfer reactions
(dark) for THERAPY
(emissive) for DIAGNOSIS and IMAGING
$^1O_2$
$^3O_2$

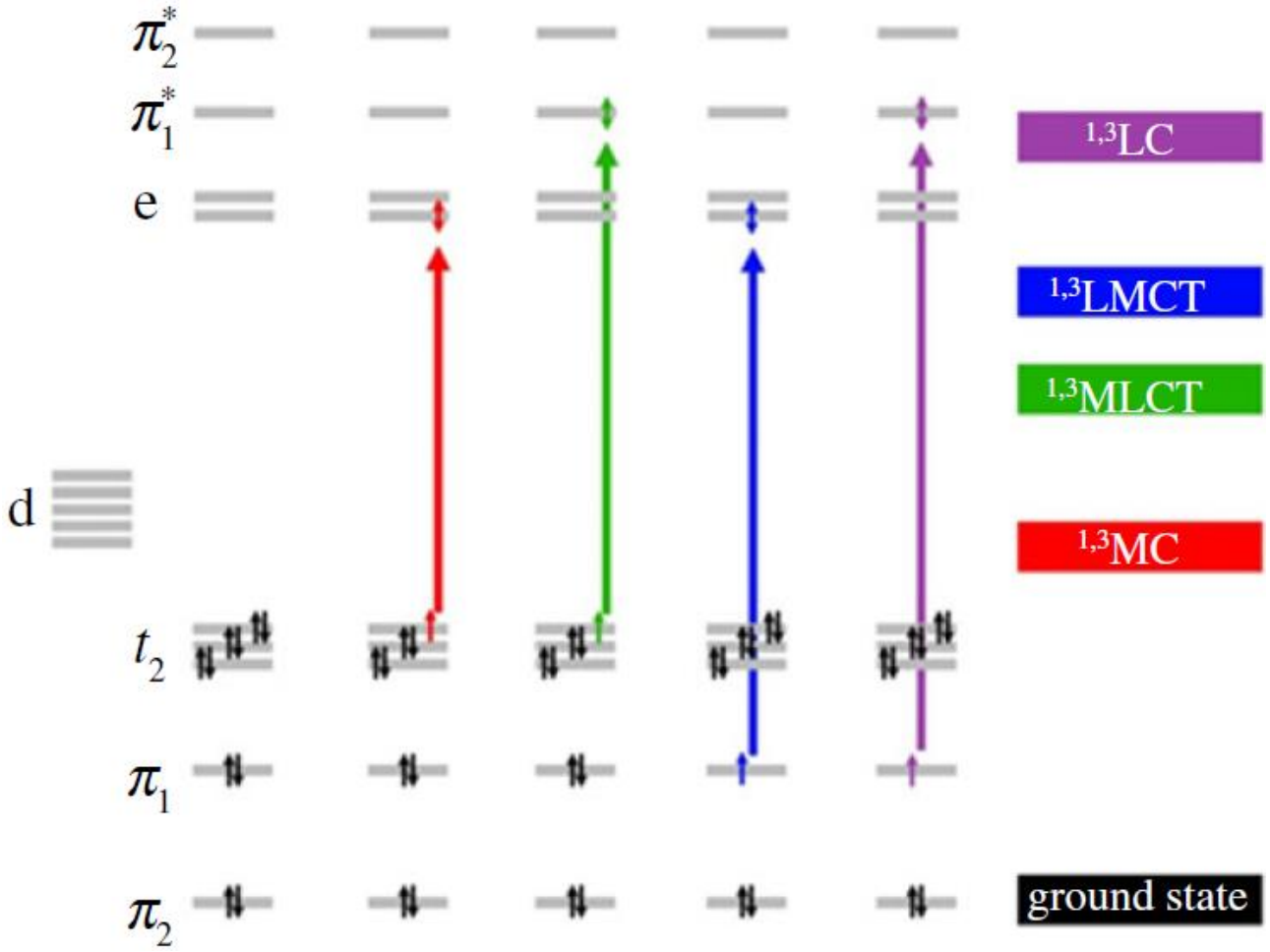
Dati 2020

Table 1. PDT agents in clinical use or in clinical trials[a].

Class	PDT agent	Metal	Stage	Excitation (nm)	Area	Cancer type
Protoporphyrin IX precursor	5-Aminolevulinic acid (Levulan®)		FDA approved	635	Global	Skin, brain, oesophagus
	Methyl aminolevulinate (Metvix®)		FDA approved	635		Skin
	Hexyl 5-aminolevulinate (Hexvix®)		FDA approved	380–450 (diagnosis)		Bladder
Porphyrin derivatives	Porfimer sodium (Photofrin®)		FDA approved	630	Global	Lung, bladder, oesophagus, bile duct, brain
	Photogem		MHRF approved	660	Russia	Respiratory and digestive tracts, urogenital
Chlorin derivatives	Temoporfin (Foscan®)		EMA approved	652	EU	Head and neck, bile duct, lung
	Ce6-PVP (Fotolon®)		Phase 2	660–670	Germany	Lung
	Radachlorin®		MHRF approved	662	Russia	Skin
	Talaporfin sodium (Laserphyrin®)		MHLW approved	664	Japan	Lung, brain
	HPPH (Photochlor®)		Phase 2	665	USA	Lung, oral cavity, oesophagus
Bacteriochlorin derivatives	Redaporfin		Phase 2	749	Portugal	Head and neck
Phthalocyanine derivatives	Silicon phthalocyanine (Pc4)		Phase 1	672	USA	Skin
Metal complex	Padoporfin (TOOKAD®)	Pd	Terminated	763	EU	Prostate
	Padeliporfin potassium (TOOKAD® Soluble)	Pd	EMA approved	753	EU	Prostate
	TLD-1433	Ru	Phase 2	520	Canada	Bladder, brain
	Motexafin lutetium (Antrin®)	Lu	Terminated	732	USA	Breast, prostate
	Rostaporfin (Purlytin®)	Sn	Phase 2/3	664	USA	Breast, bile duct, ovarian, colon

[a]Data from clinicaltrials.gov.

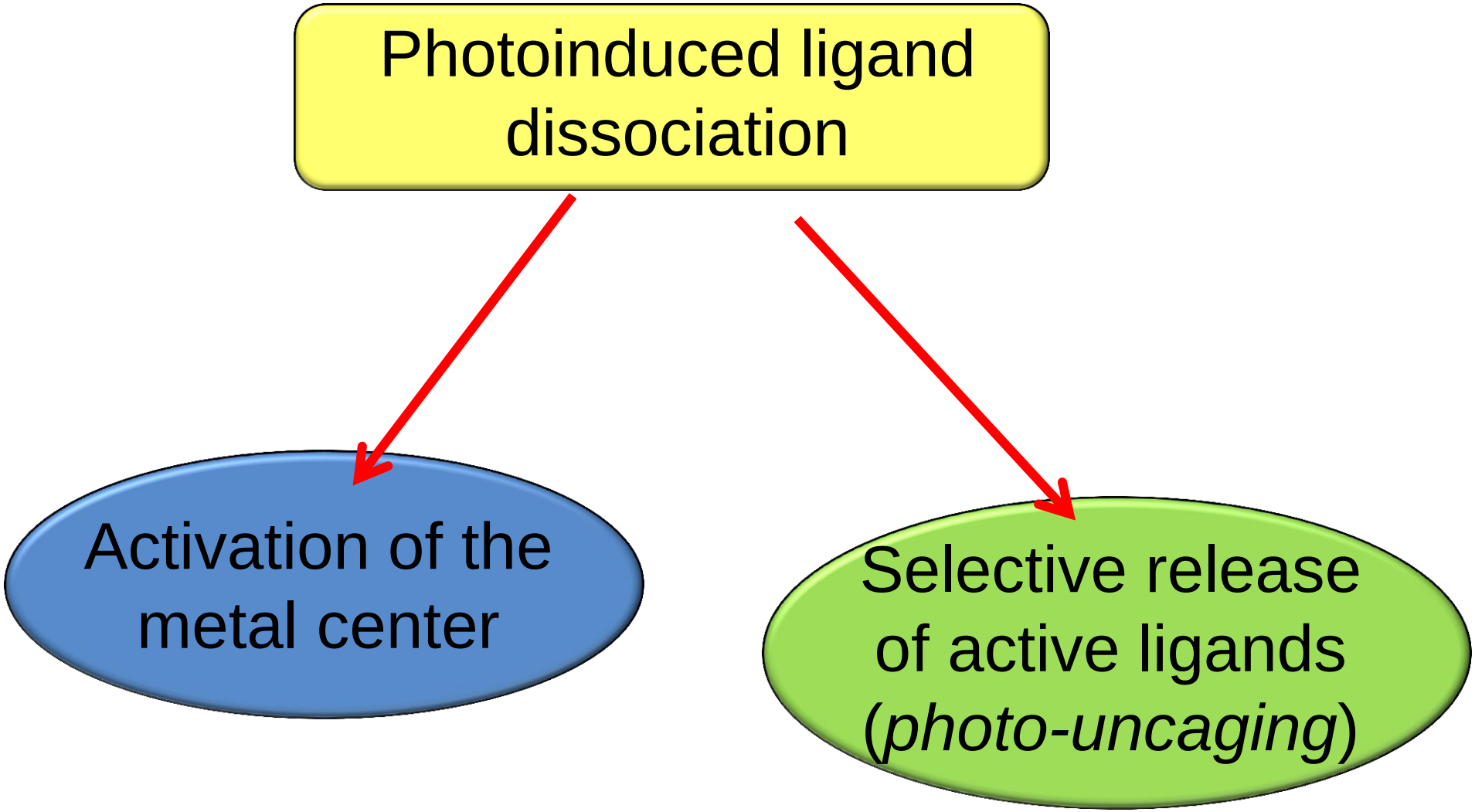
Photoactivatable metal compounds



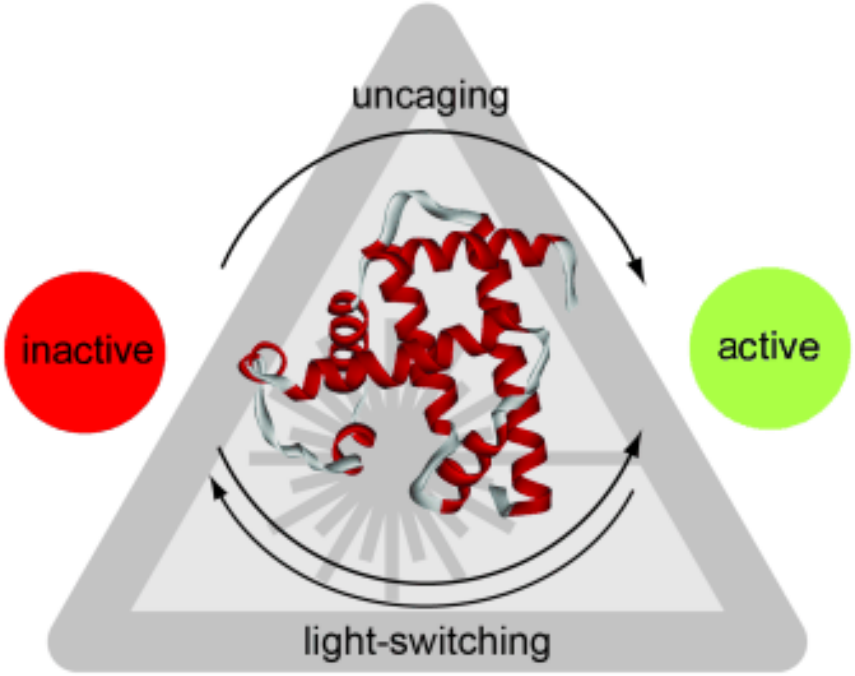
Photoactivatable metal compounds

These complexes are inert and non-toxic to cells in the dark.
Upon irradiation at the tumor site, they undergo various photochemical reactions, including isomerization, substitution, and reduction.

The photoactivation pathway of metal complexes does not rely on O_2, which is a significant advantage over the photosensitizers used in current PDT. However, photoactivation – contrary to PDT – is a stoichiometric proces.

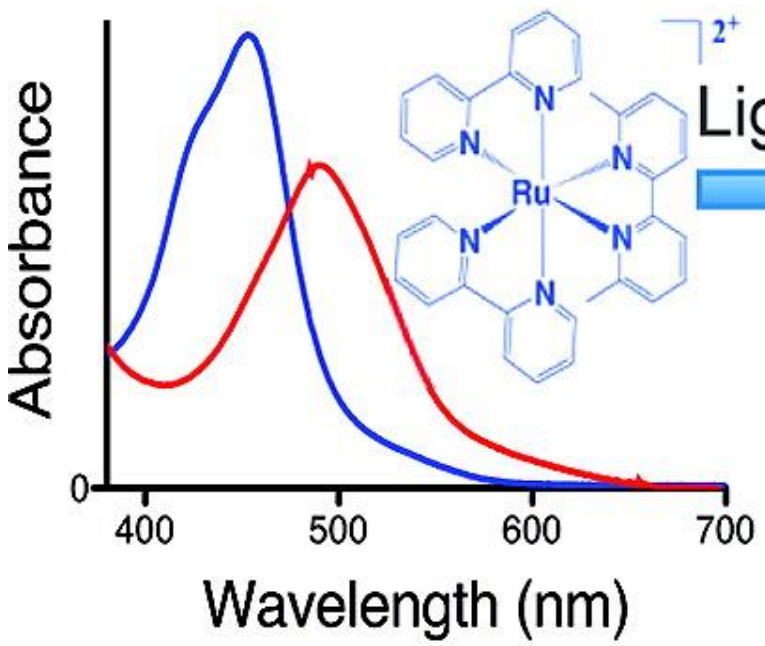

Photoinduced ligand dissociation
Activation of the metal center
Selective release of active ligands (*photo-uncaging*)

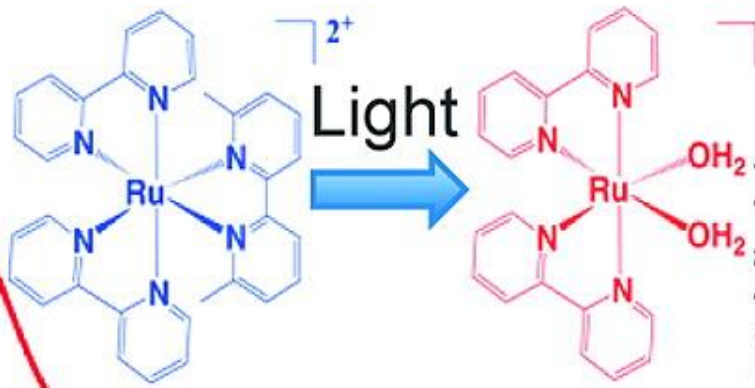
Caged compounds and photo-uncaging

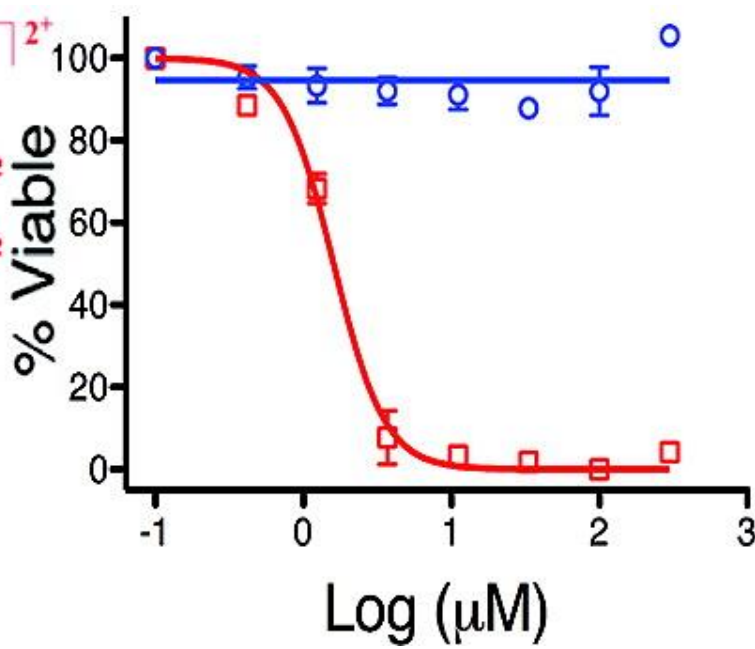


Photolabile protecting groups, attached to a defined position of a molecule, can be used to gain spatio-temporal control over the concentration of the active form of a molecule.

Photoactivatable Ru compounds

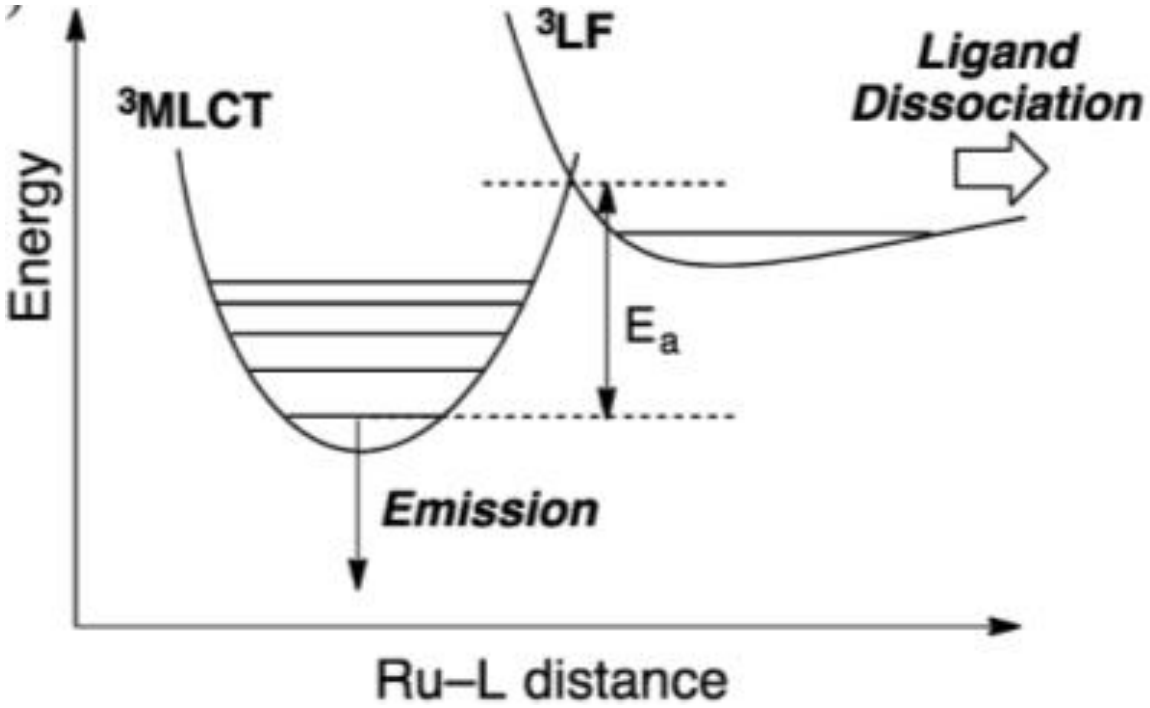


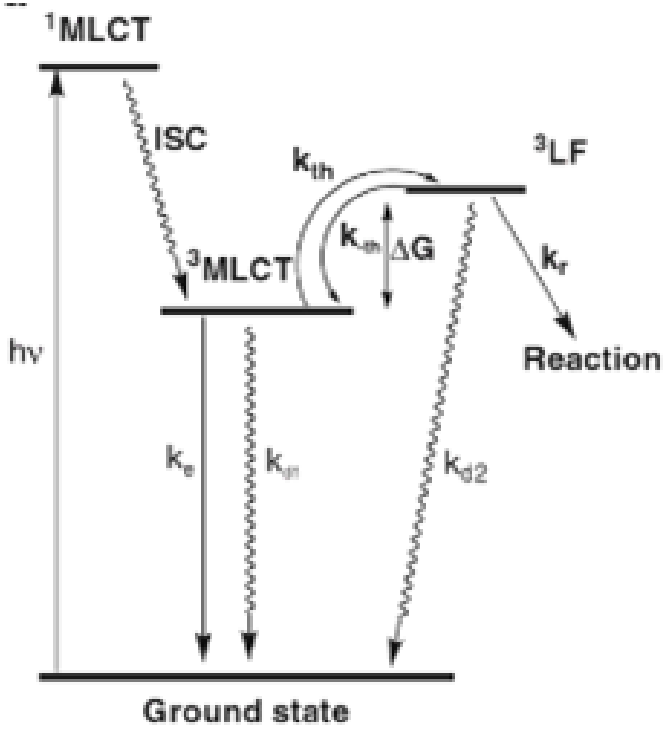


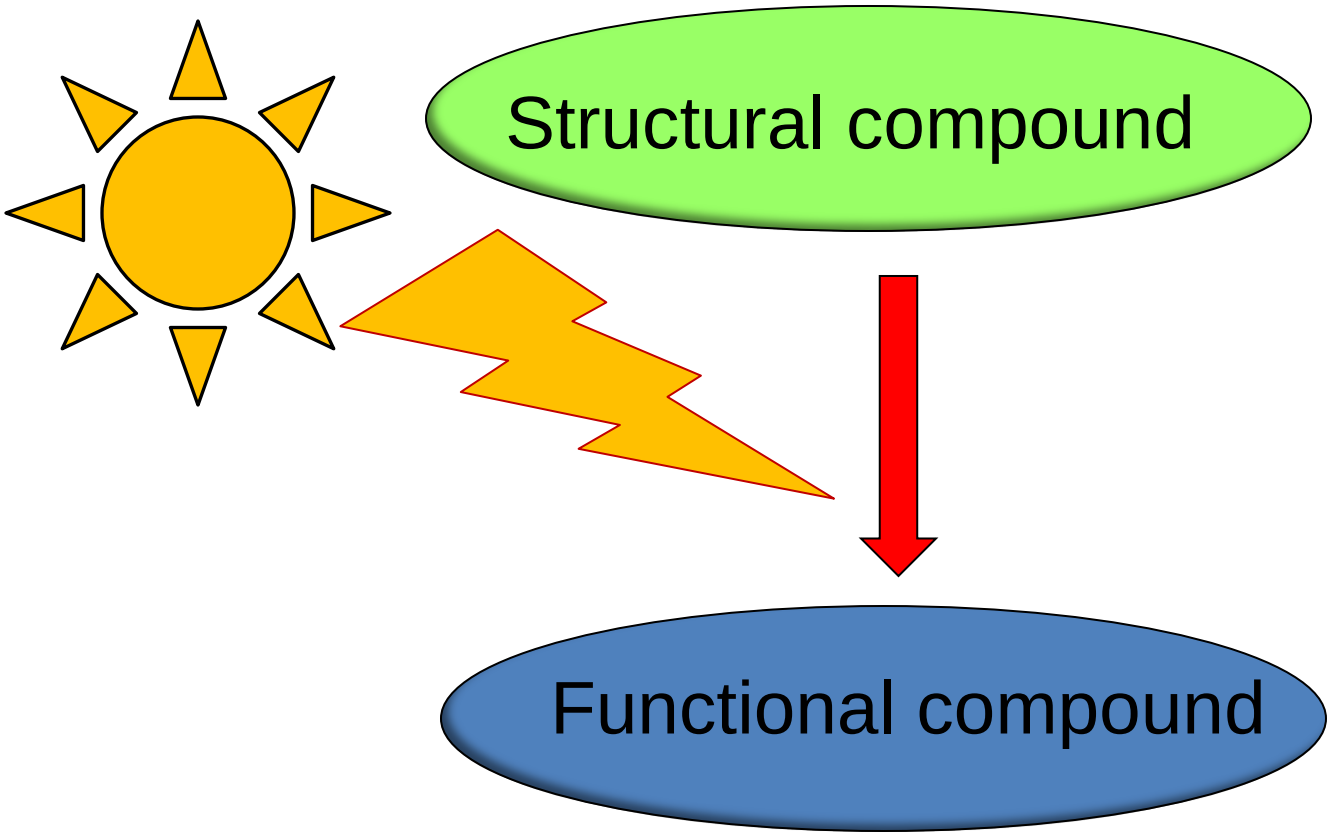


Phototoxicity Index, PI

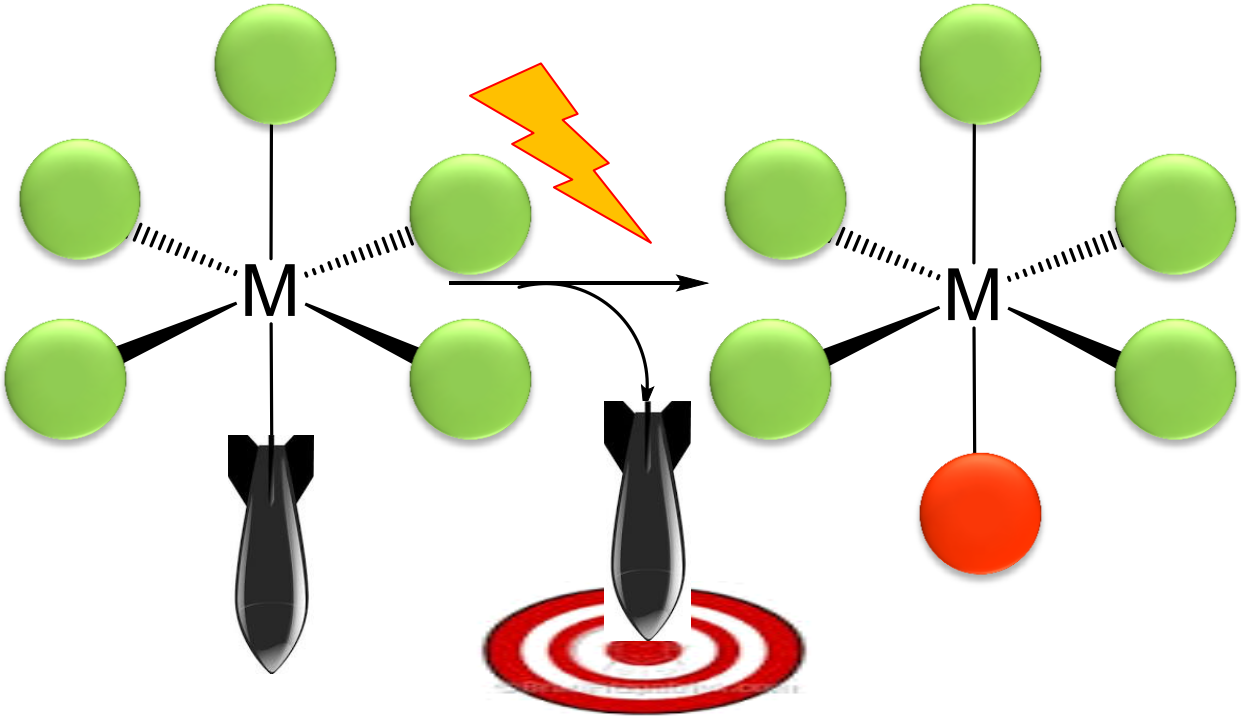
Photoactivatable Ru compounds






Structural compound
Functional compound

Metal compounds for the delivery of active molecules

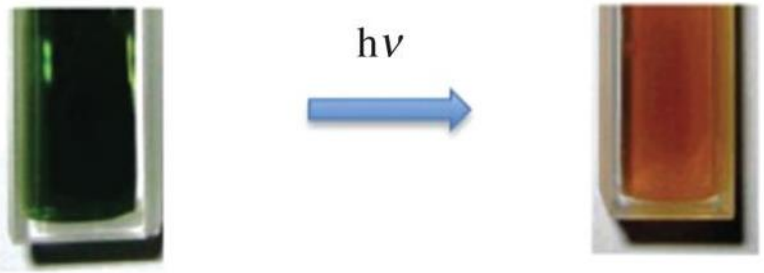


= NO, CO, 4-aminopyridine (4-AP, K^+ channel blocker), γ-aminobutyric acid (GABA, a neurotransmitter),…

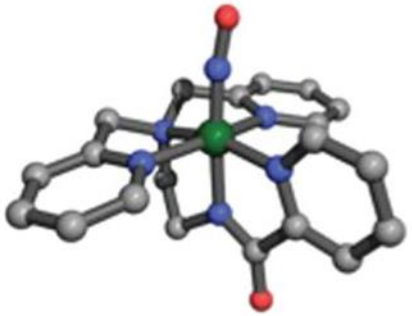
Caged compounds and photo-uncaging

NO Releasing Molecules = NORM
CO Releasing Molecules = CORM

Photo-NORM
Photo-CORM



$[Mn(PaPy_3)(NO)]^+$



$[Mn(PaPy_3)(H_2O)]^+$

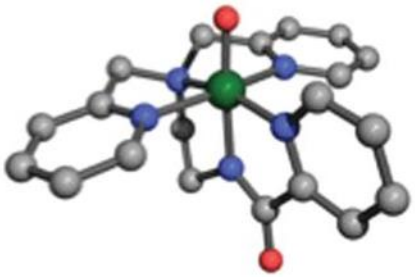
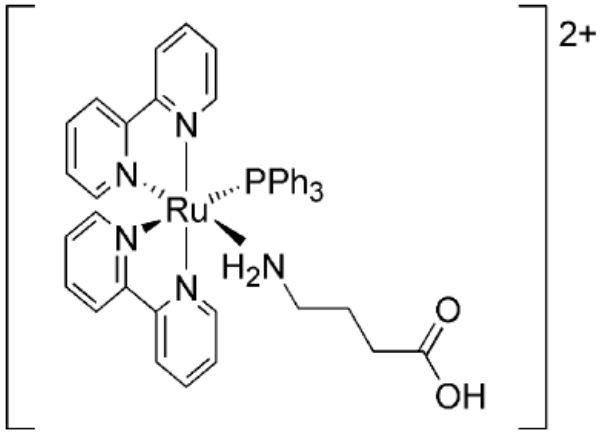
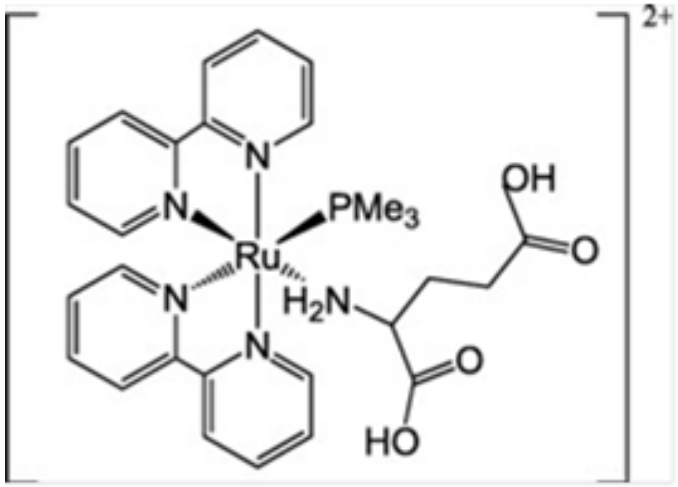
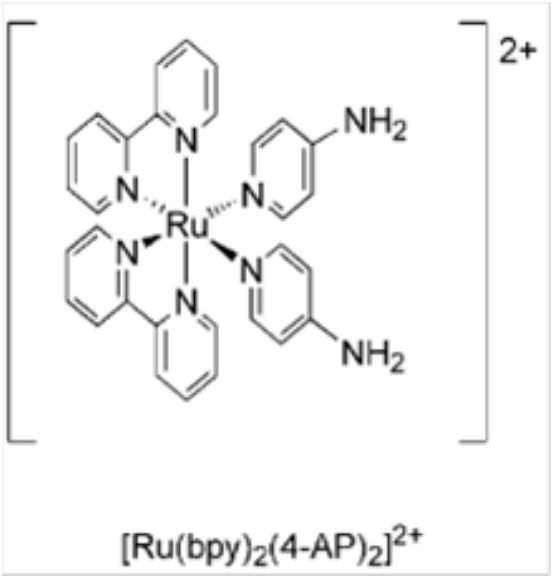


Photo-release of neurotransmitters



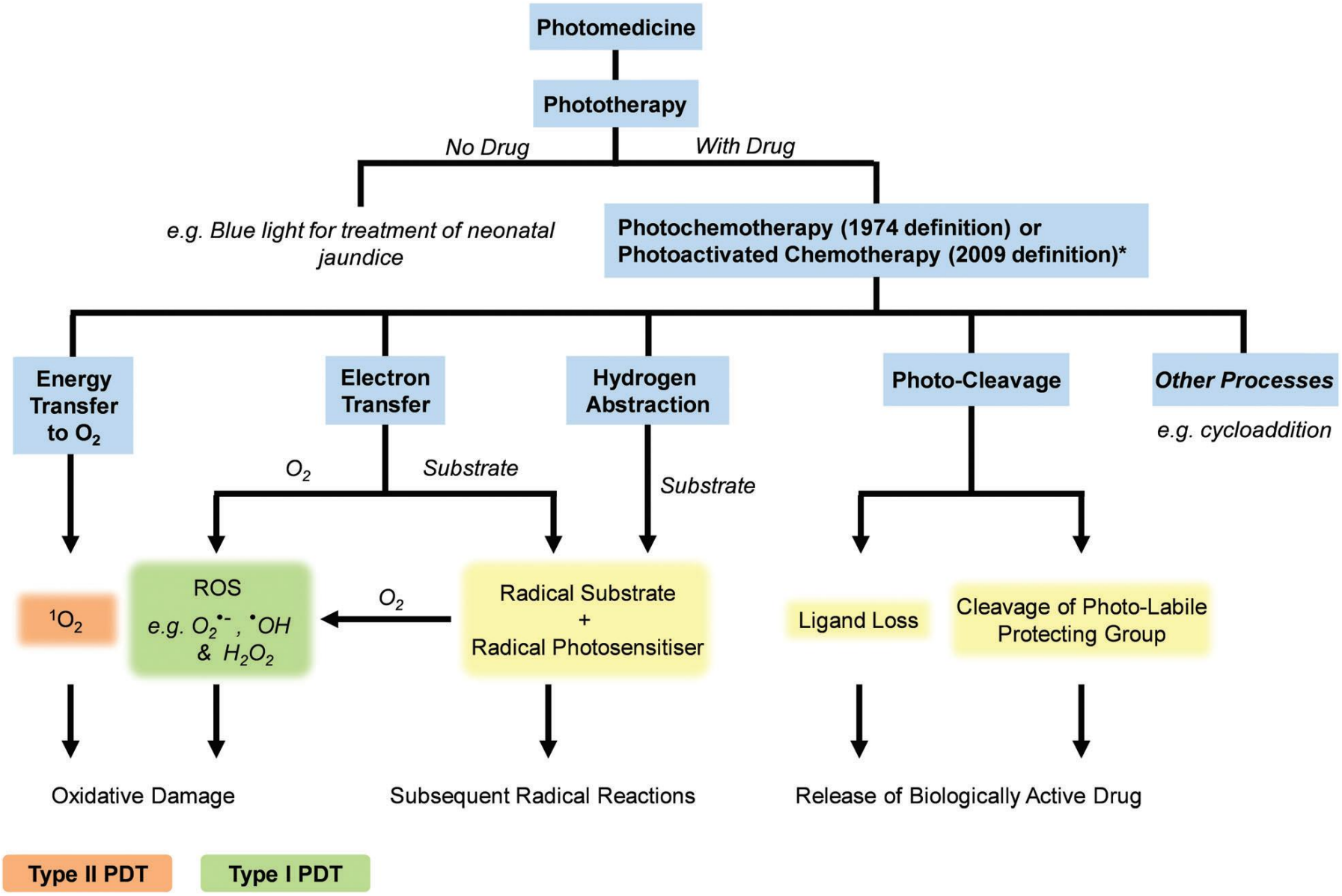
$[Ru(bpy)_2(PPh_3)(GABA)]^{2+}$





$[Ru(bpy)_2(4\text{-}AP)_2]^{2+}$

GABA = γ-aminobutyric acid: inhibitory neurotransmitter
Glutamic acid: excitatory neurotransmitter
4-AP = 4-aminopyridine: K^+ channel blocker


Photomedicine
Phototherapy
No Drug
With Drug
e.g. Blue light for treatment of neonatal jaundice
Photochemotherapy (1974 definition) or Photoactivated Chemotherapy (2009 definition)*
Energy Transfer to O_2
Electron Transfer
Hydrogen Abstraction
Photo-Cleavage
Other Processes
e.g. cycloaddition
O_2
Substrate
Substrate
$^1O_2$
ROS
e.g. $O_2^{\bullet-}$, $^{\bullet}OH$ & H_2O_2
O_2
Radical Substrate + Radical Photosensitiser
Ligand Loss
Cleavage of Photo-Labile Protecting Group
Oxidative Damage
Subsequent Radical Reactions
Release of Biologically Active Drug
Type II PDT
Type I PDT