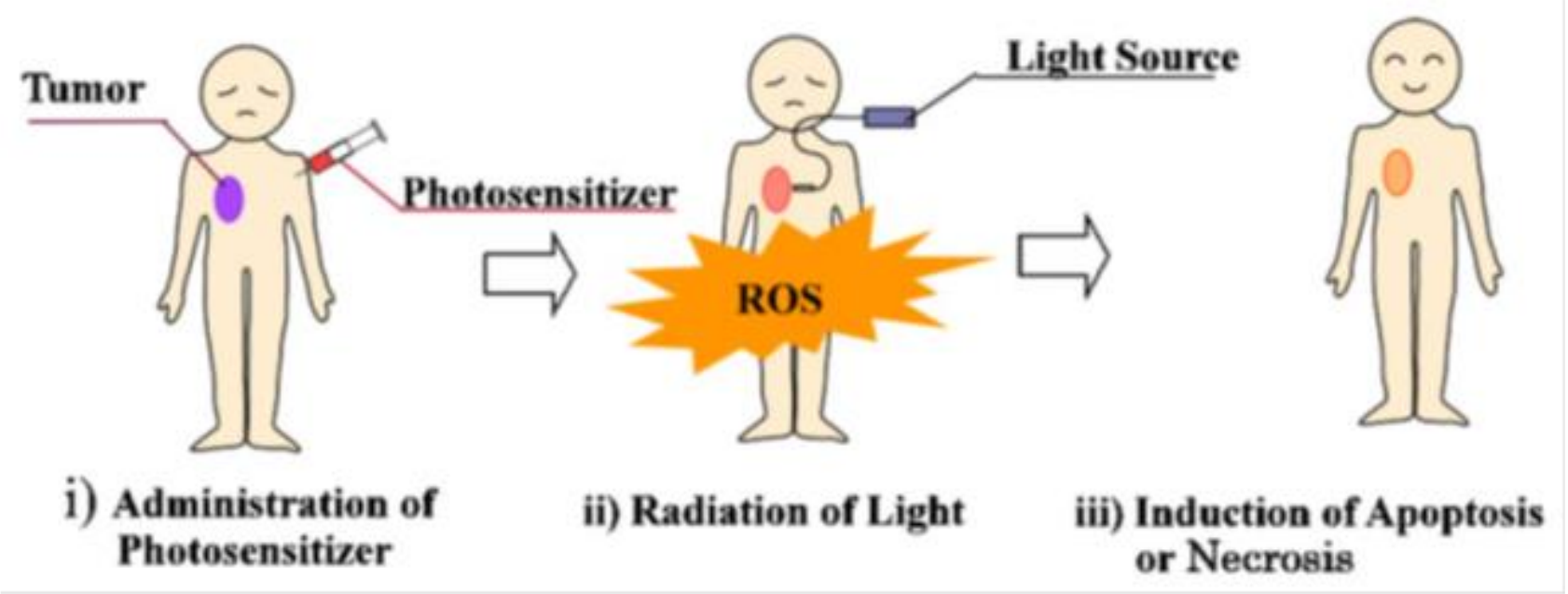
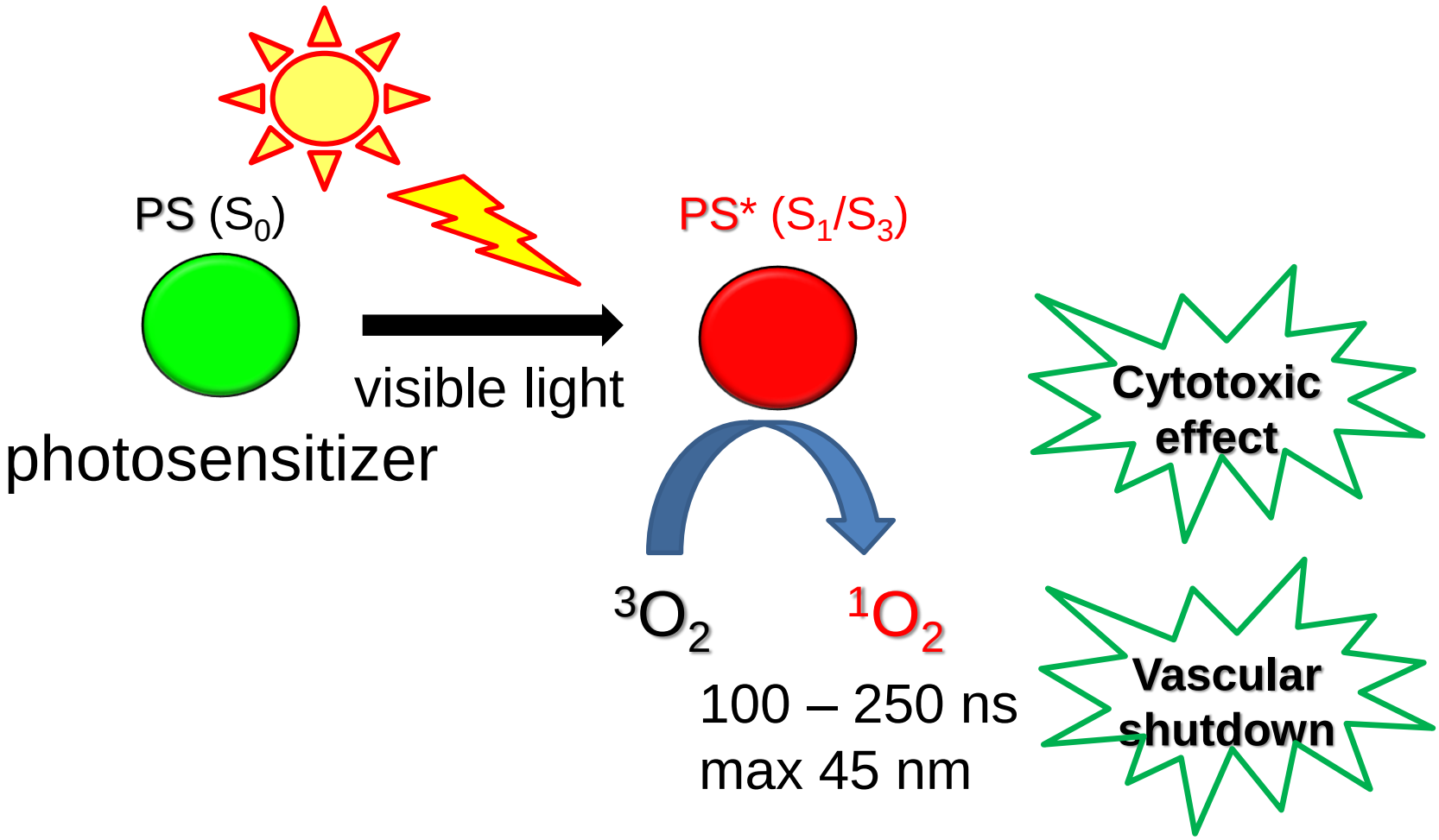
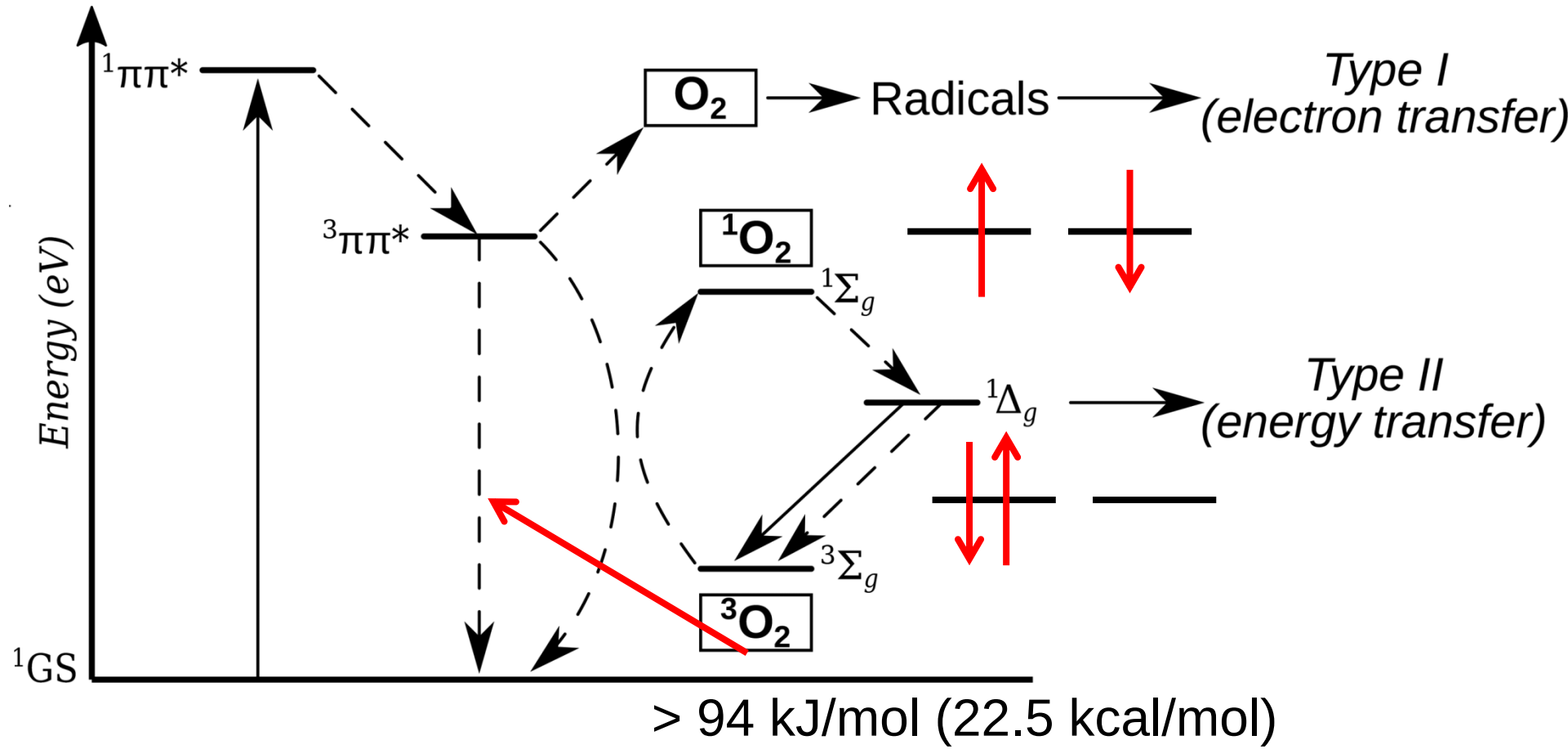
Terapia Fotodinamica (PDT)
terapia ternaria

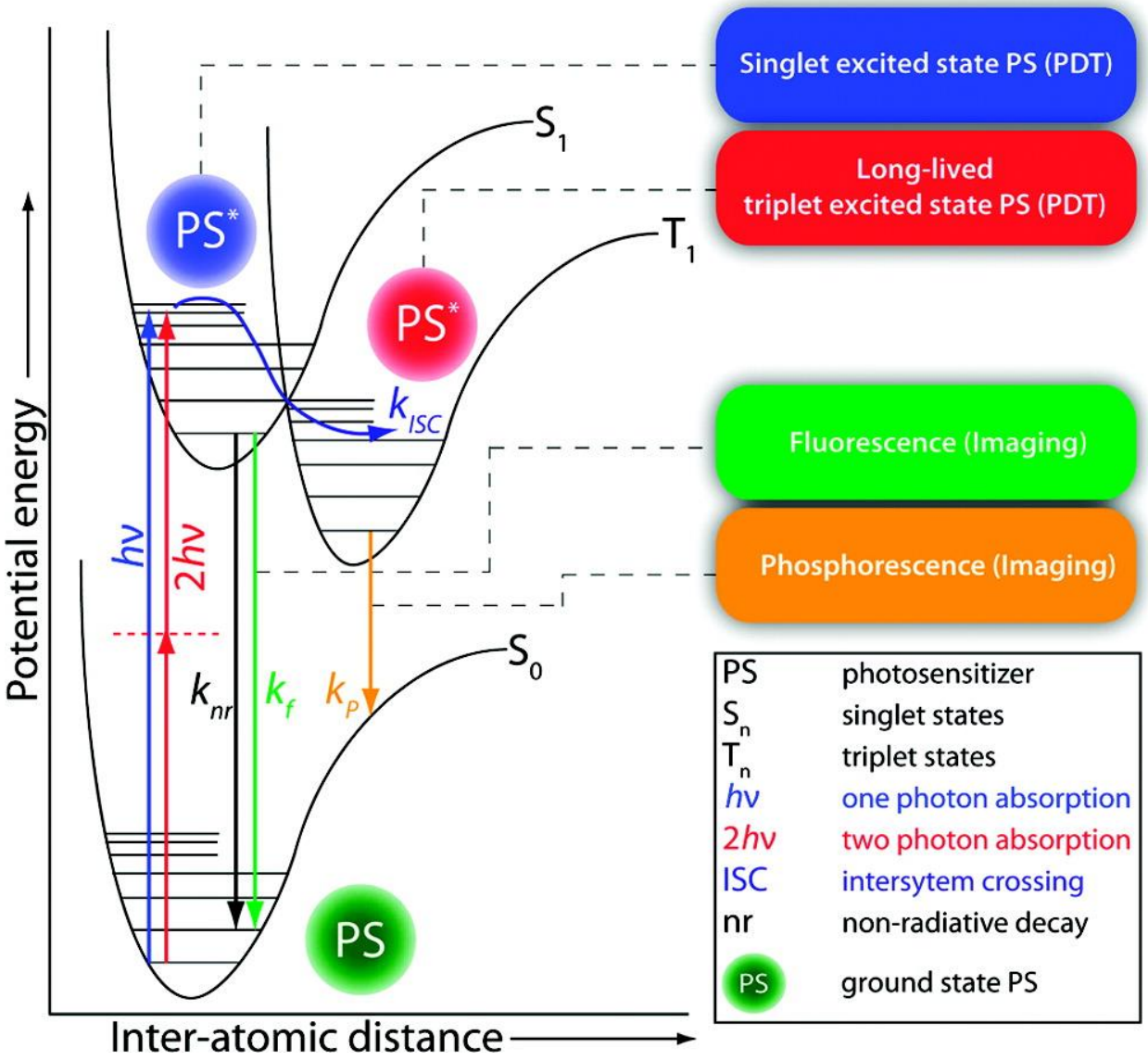


Controllo spazio-temporale

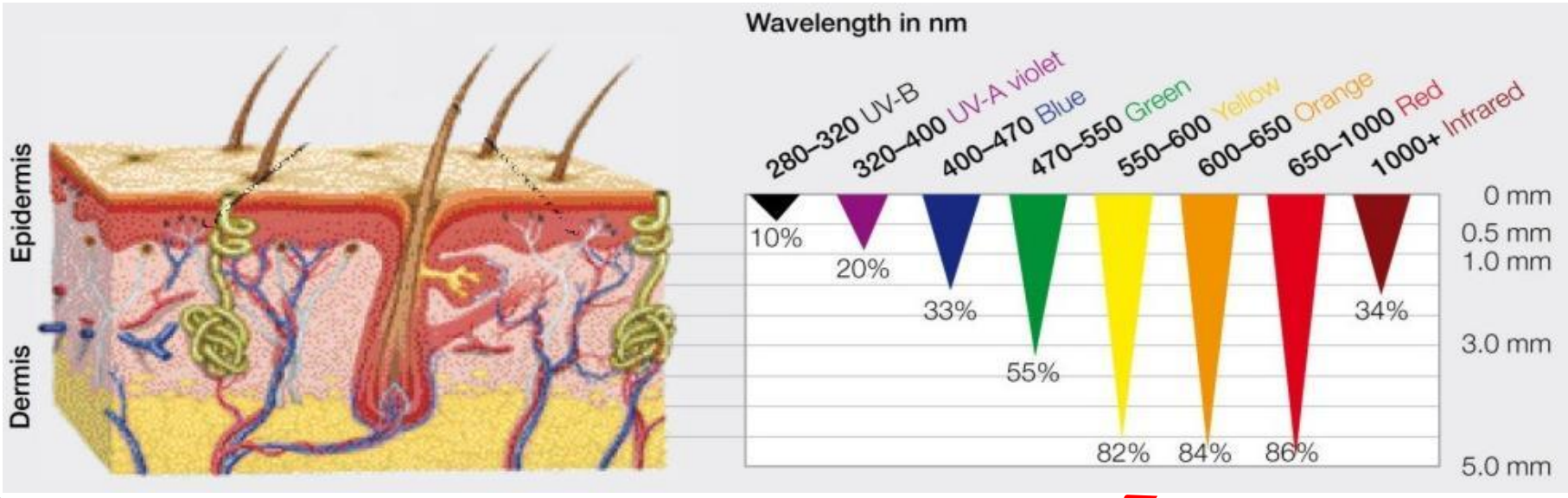
Terapia Fotodinamica (PDT)




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

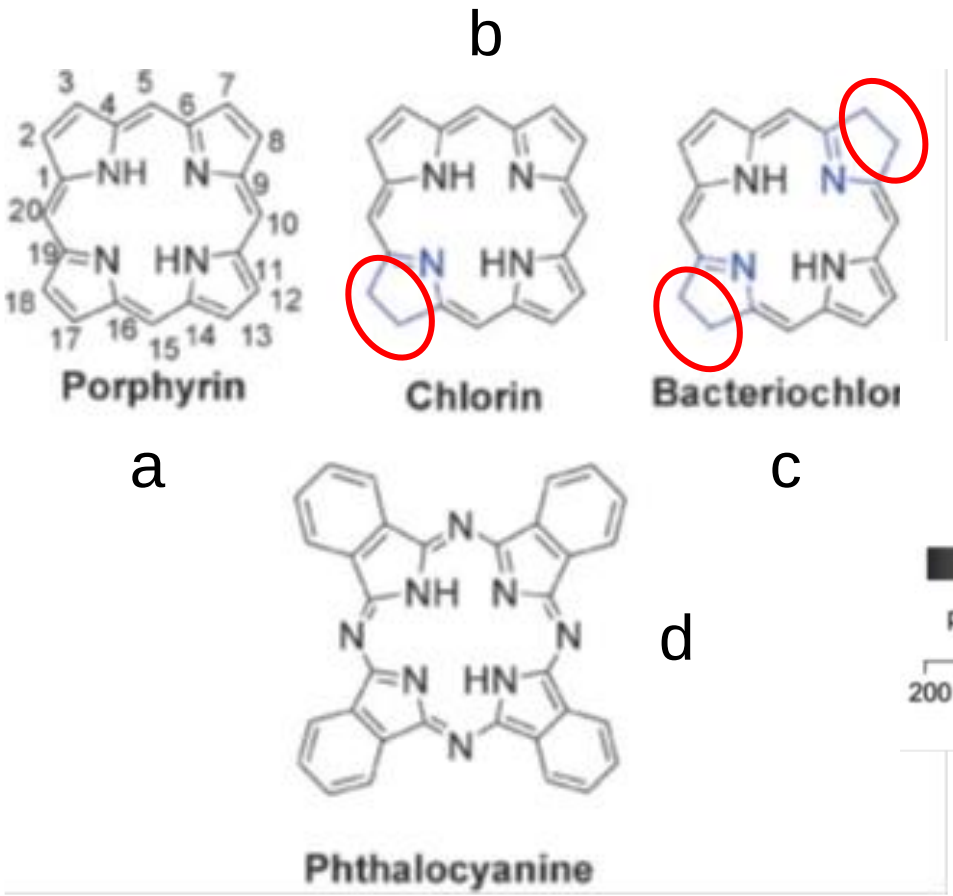
ΔE between $^1O_2$ and $^3O_2$ = 22.5 kcal/mol

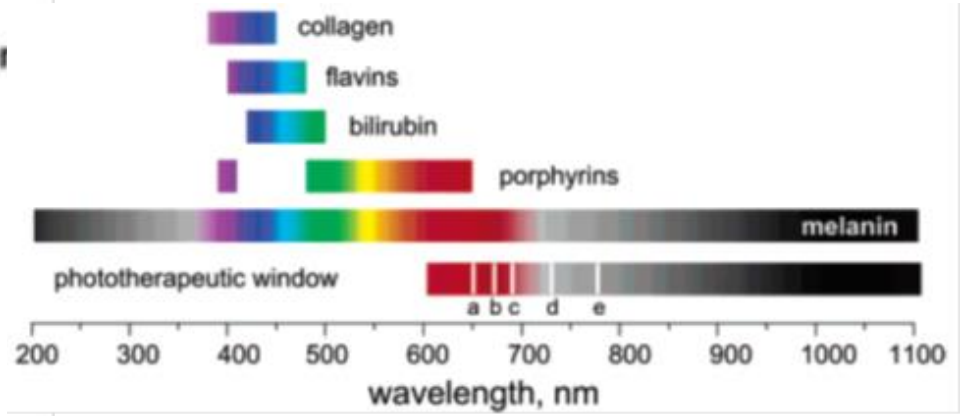
This energy gap is compatible with photosensitizers that have absorption maxima up to over 800 nm (their triplet excited state is still higher in energy than the ground state of $^3O_2$.

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

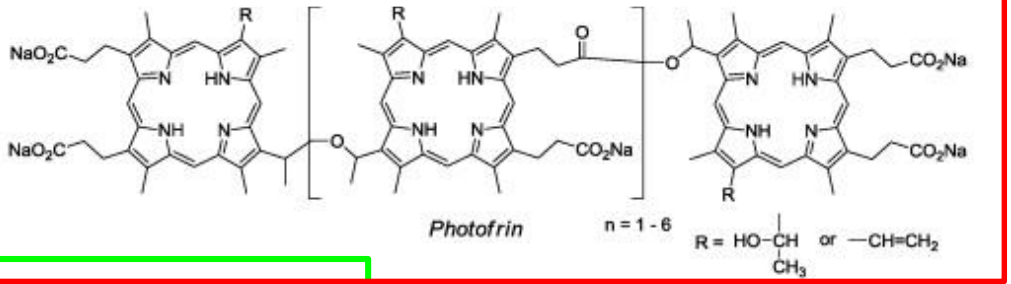
Macrocicli tetrapirrolici come PS



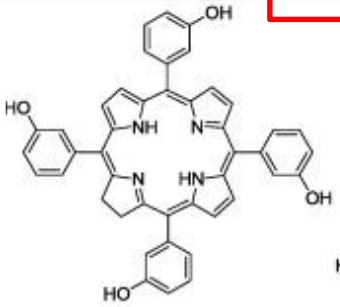


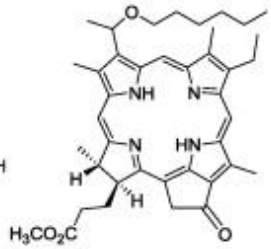
Fotosensibilizzatori per PDT di prima e seconda generazione

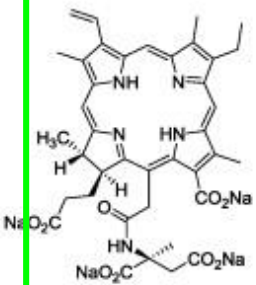
λ = 652
ε = 3×10^4 M^{-1}cm^{-1}

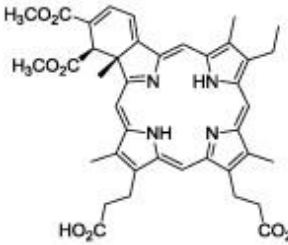


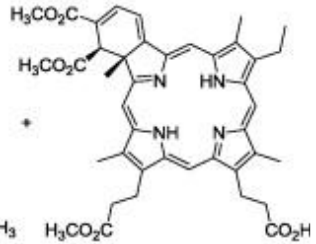
λ = 630
ε = 1170 M^{-1}cm^{-1}

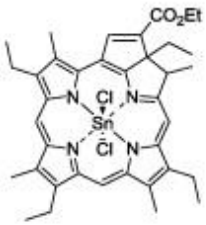

Foscan

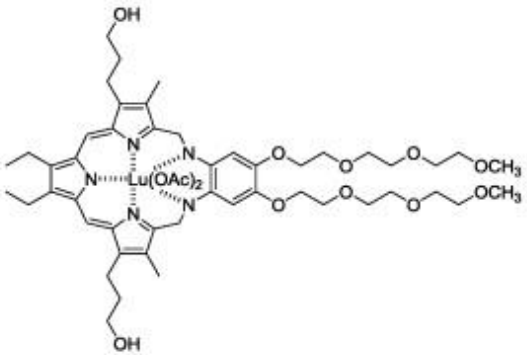

Photochlor

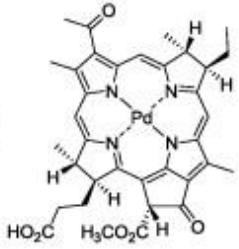

Talaporfin sodium

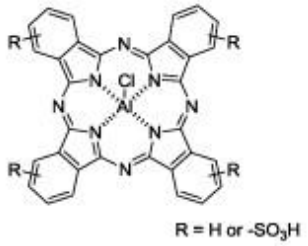



Visudyne


Purlytin


Lutrin

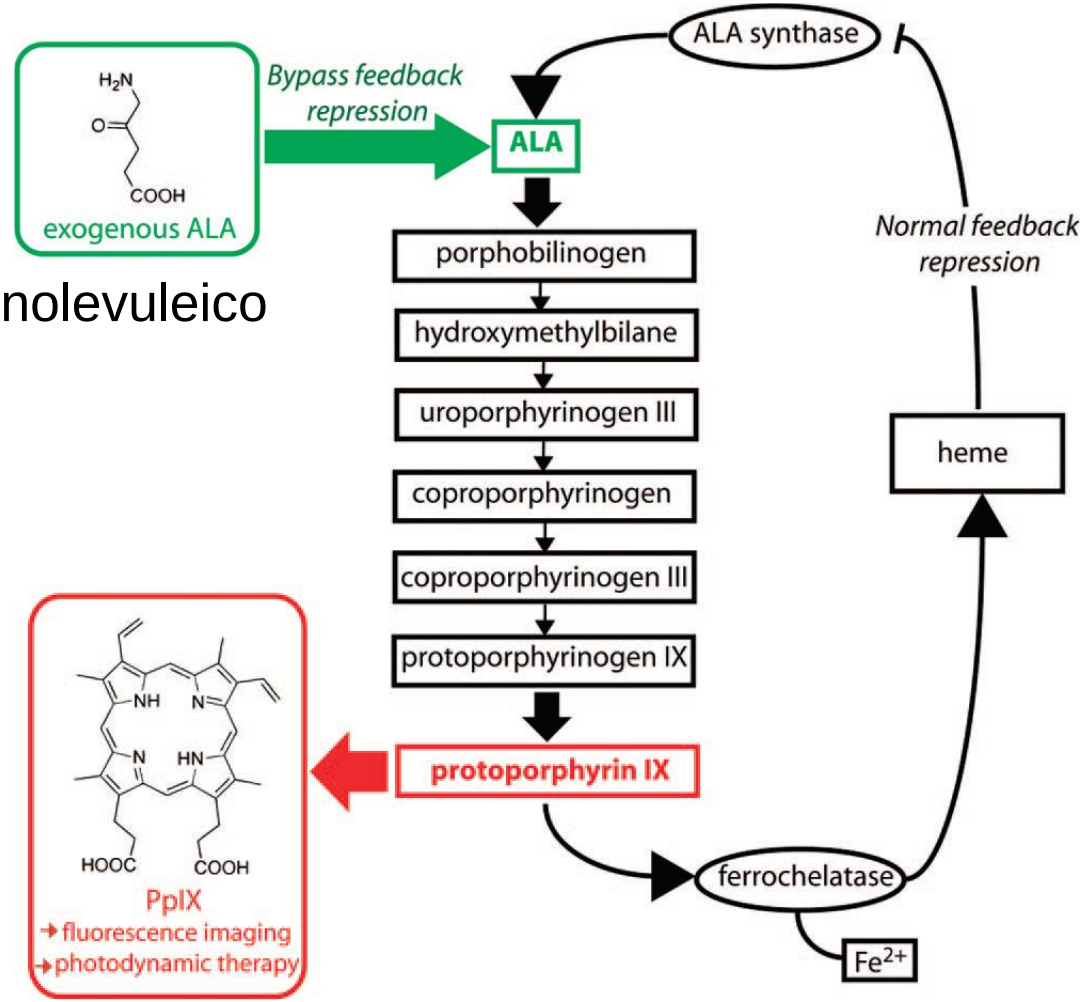

Tookad

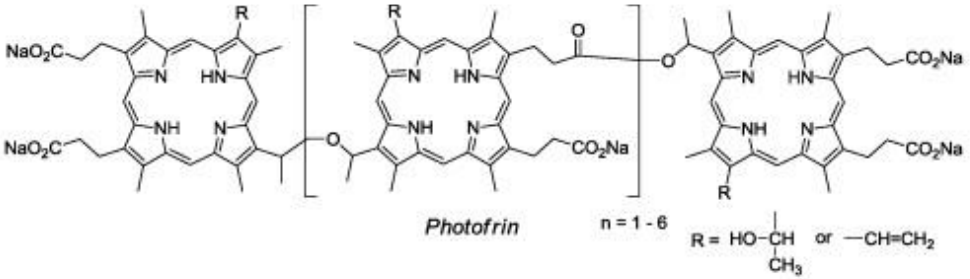


Photosens

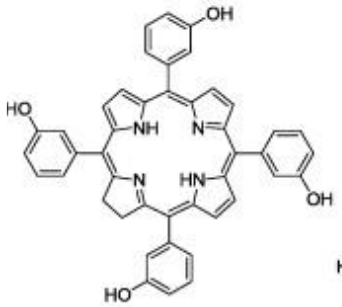
Tumori della pelle non-pigmentati: ALA-PDT

acido 5-aminolevuleico

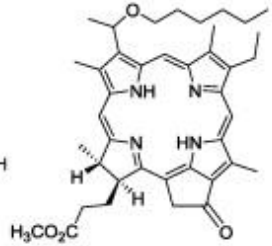




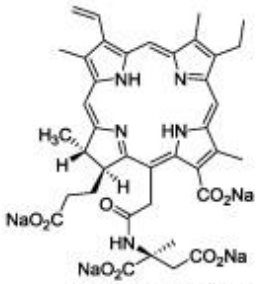
Photofrin



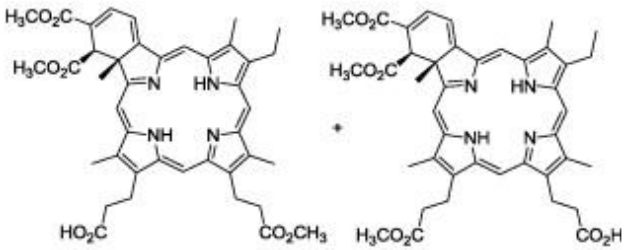
Foscan



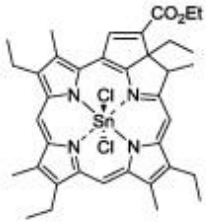
Photochlor



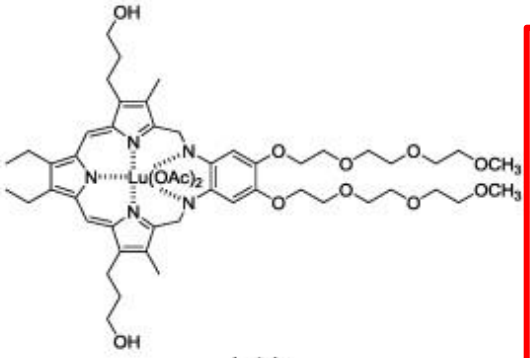
Talaporfin sodium



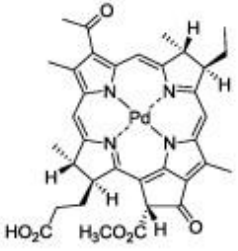
Visudyne



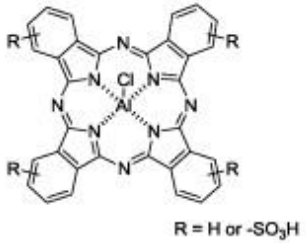
Purlytin



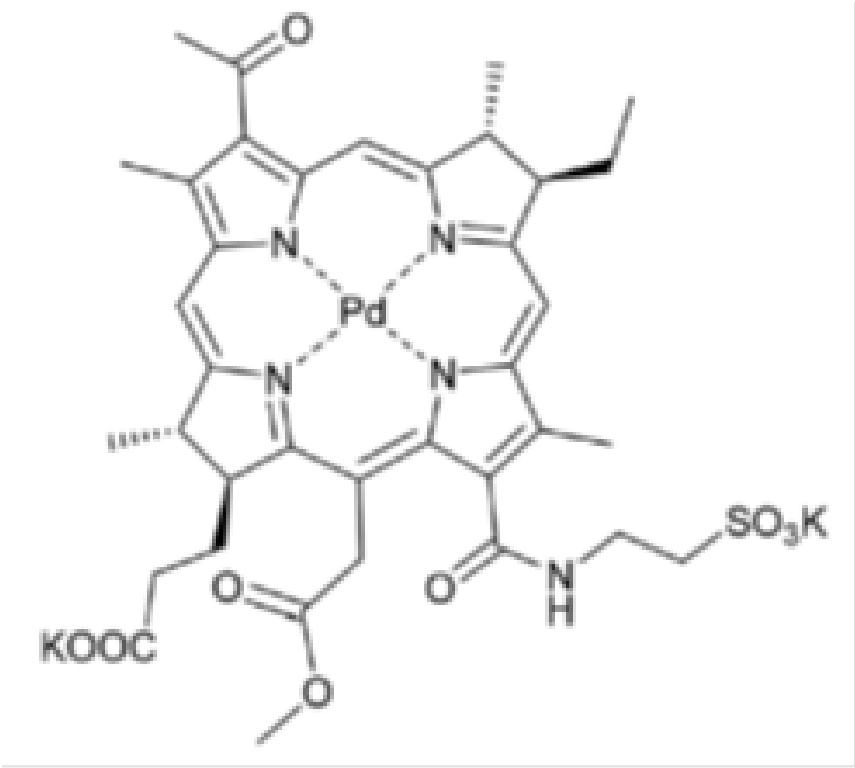
Lutrin



Tookad

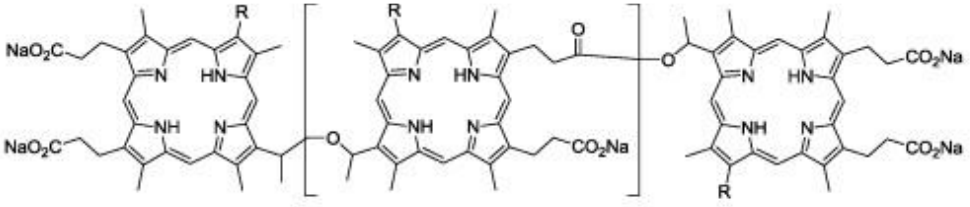


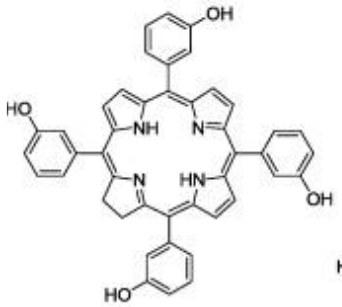
Photosens

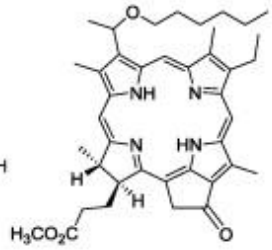


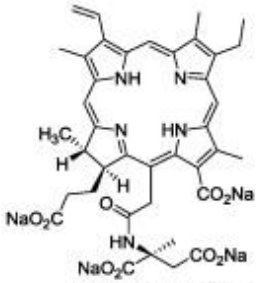
TOOKAD-solubile

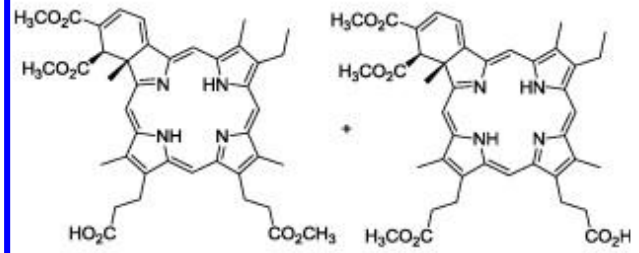
(palladio-batteriofeoforbide)



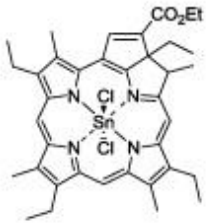

Foscan

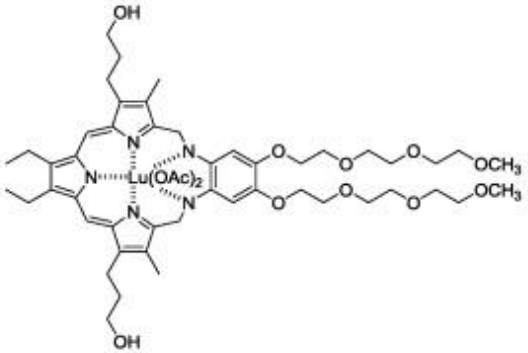

Photochlor

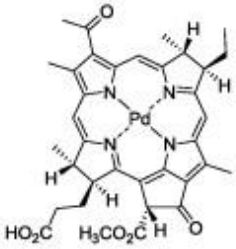

Talaporfin sodium

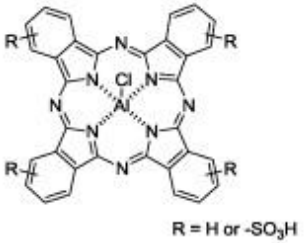

Visudyne

degenerazione maculare senile


Purlytin

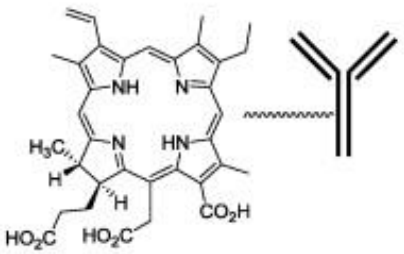

Lutrin


Tookad

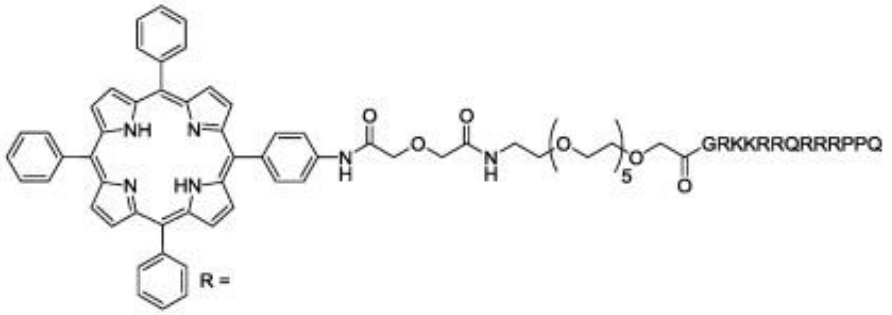


Photosens

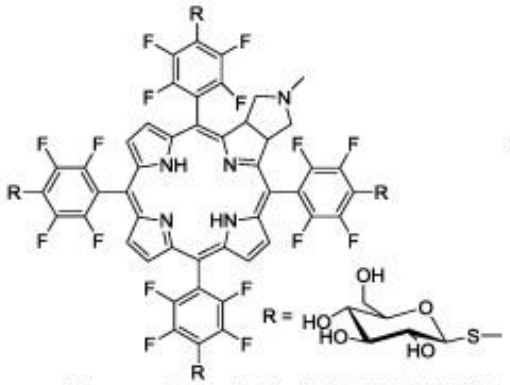
Fotosensibilizzatori per PDT di terza generazione (targeted)



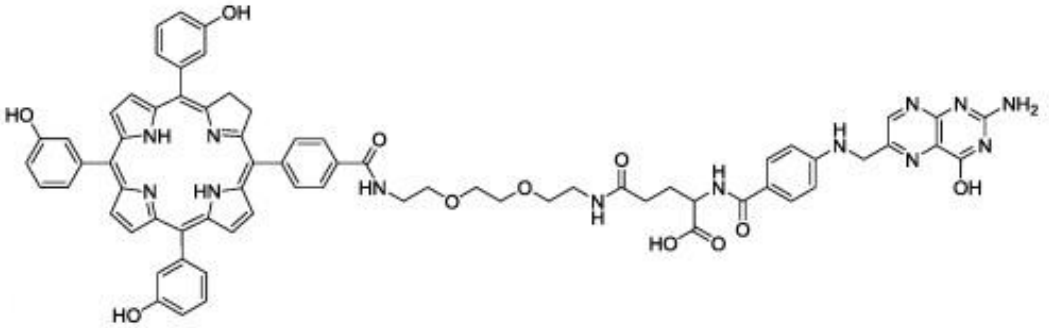
IgG conjugated chlorin



HIV-1 Tat peptide conjugated porphyrin

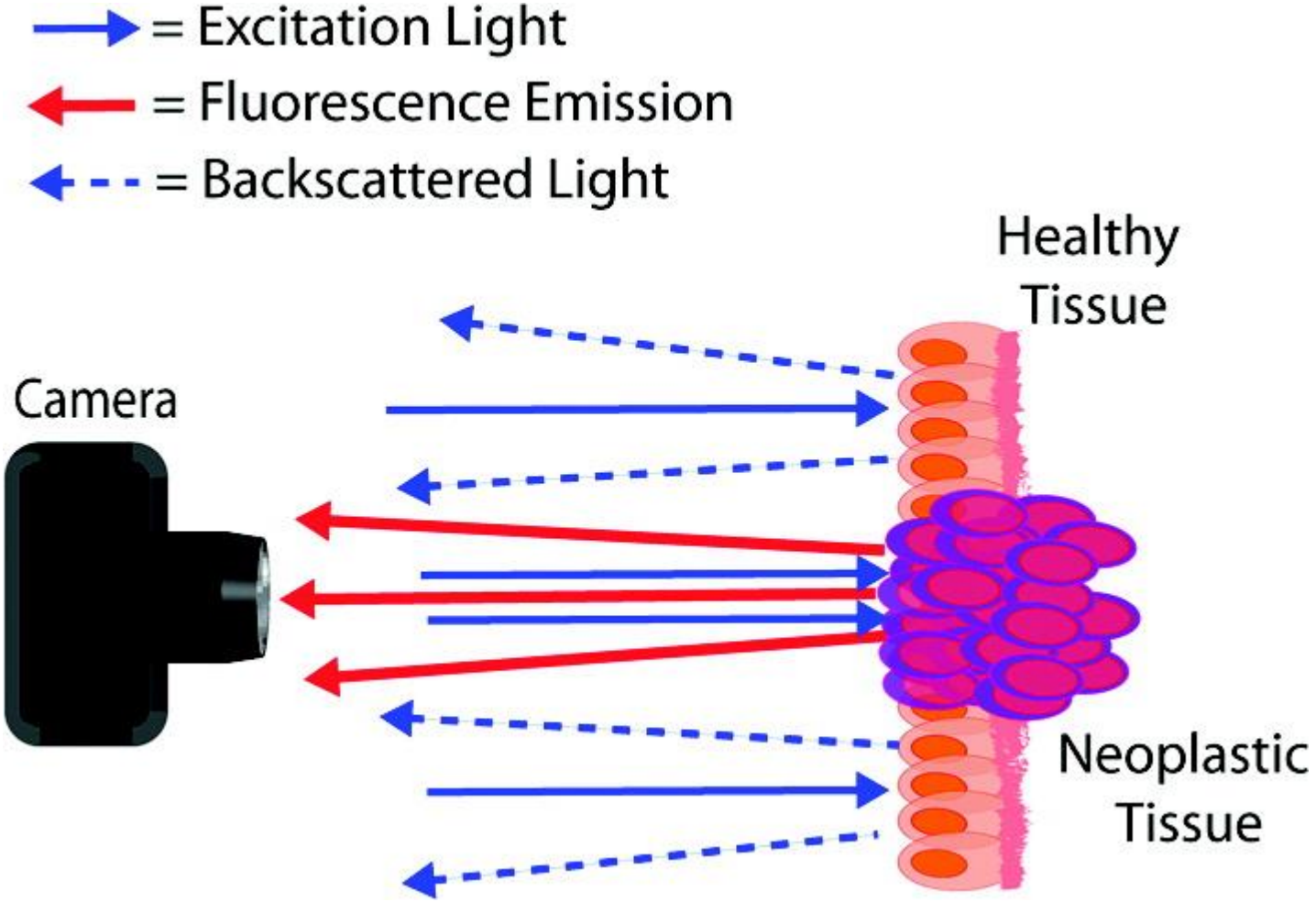


Glycoconjugated chlorin (H_2TFPC-SGlc)

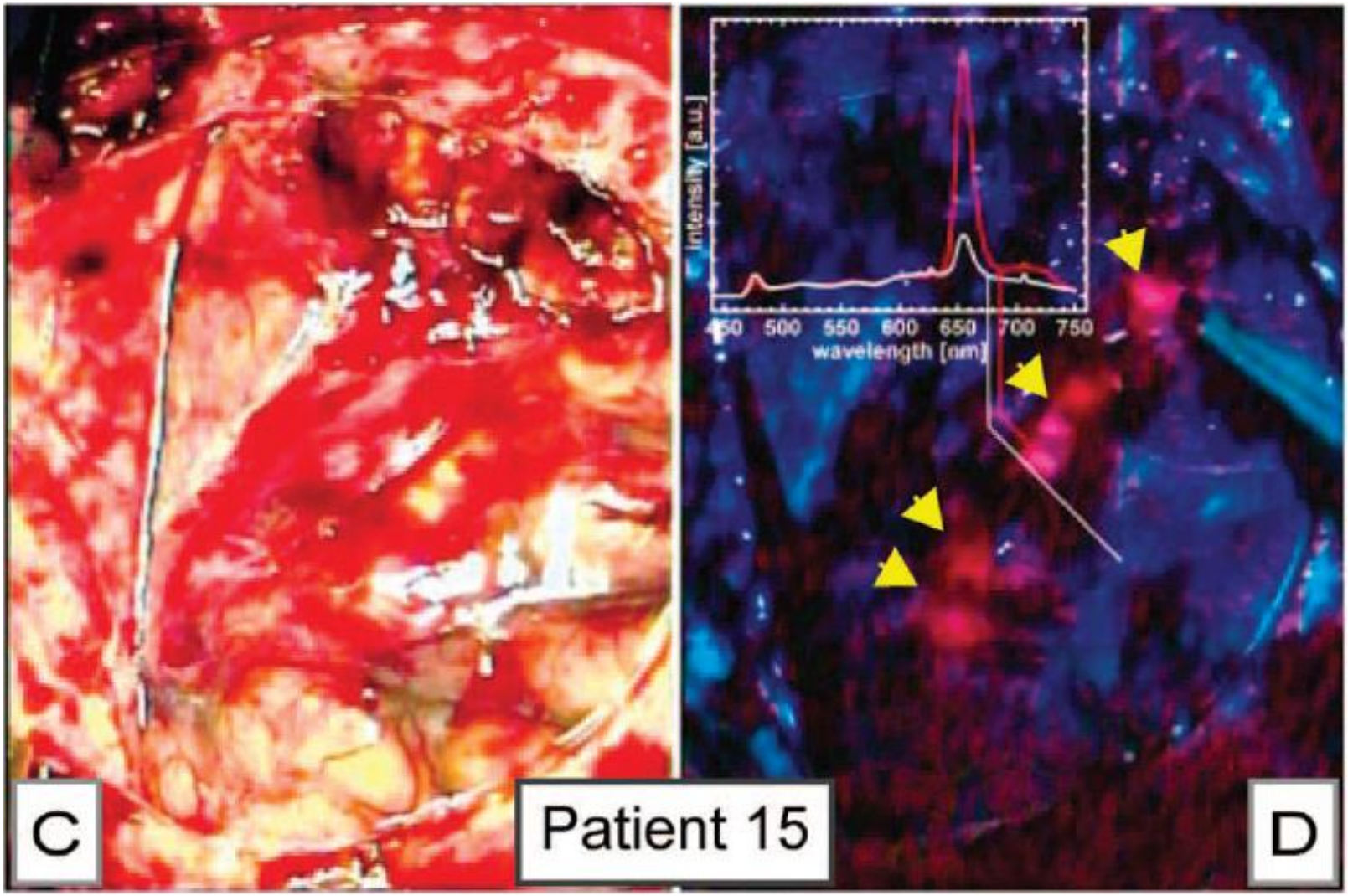


Folate conjugated temoporfin

Tumor margin resection with *tumor avid* PS's

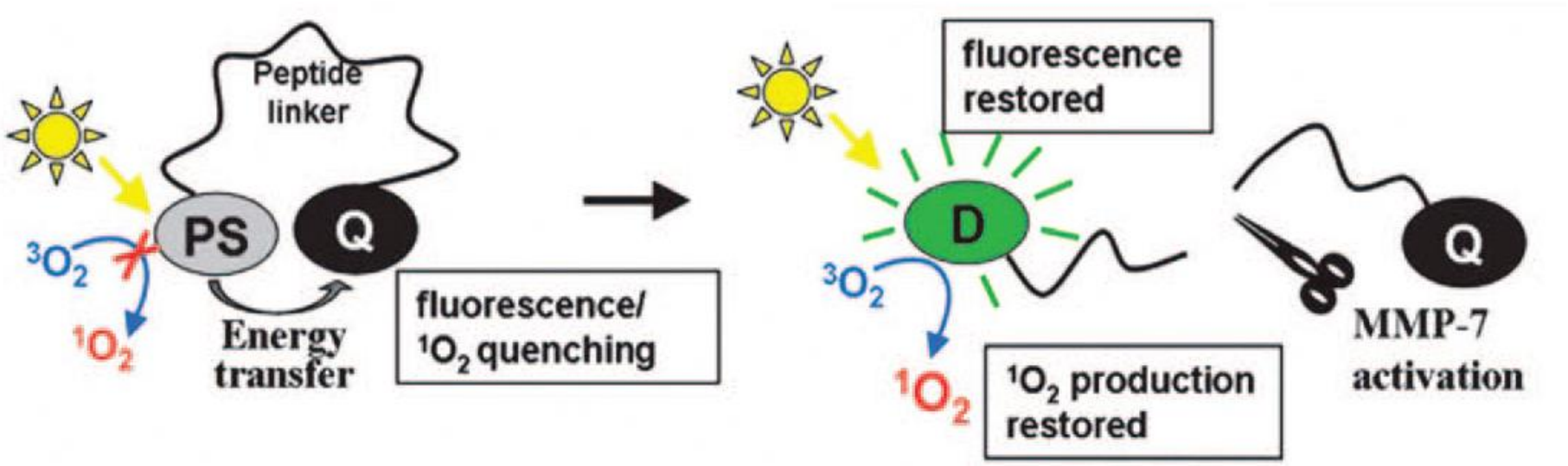


Brain tumor, patient treated with Foscan

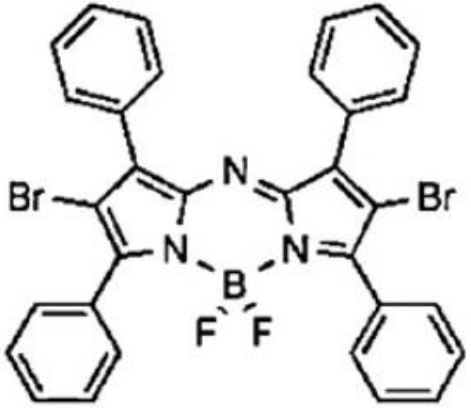


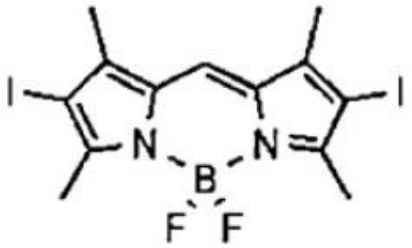
Blue light

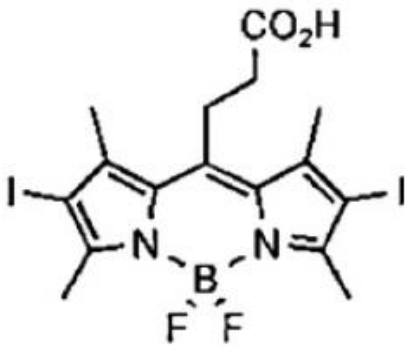
Site-activated constructs



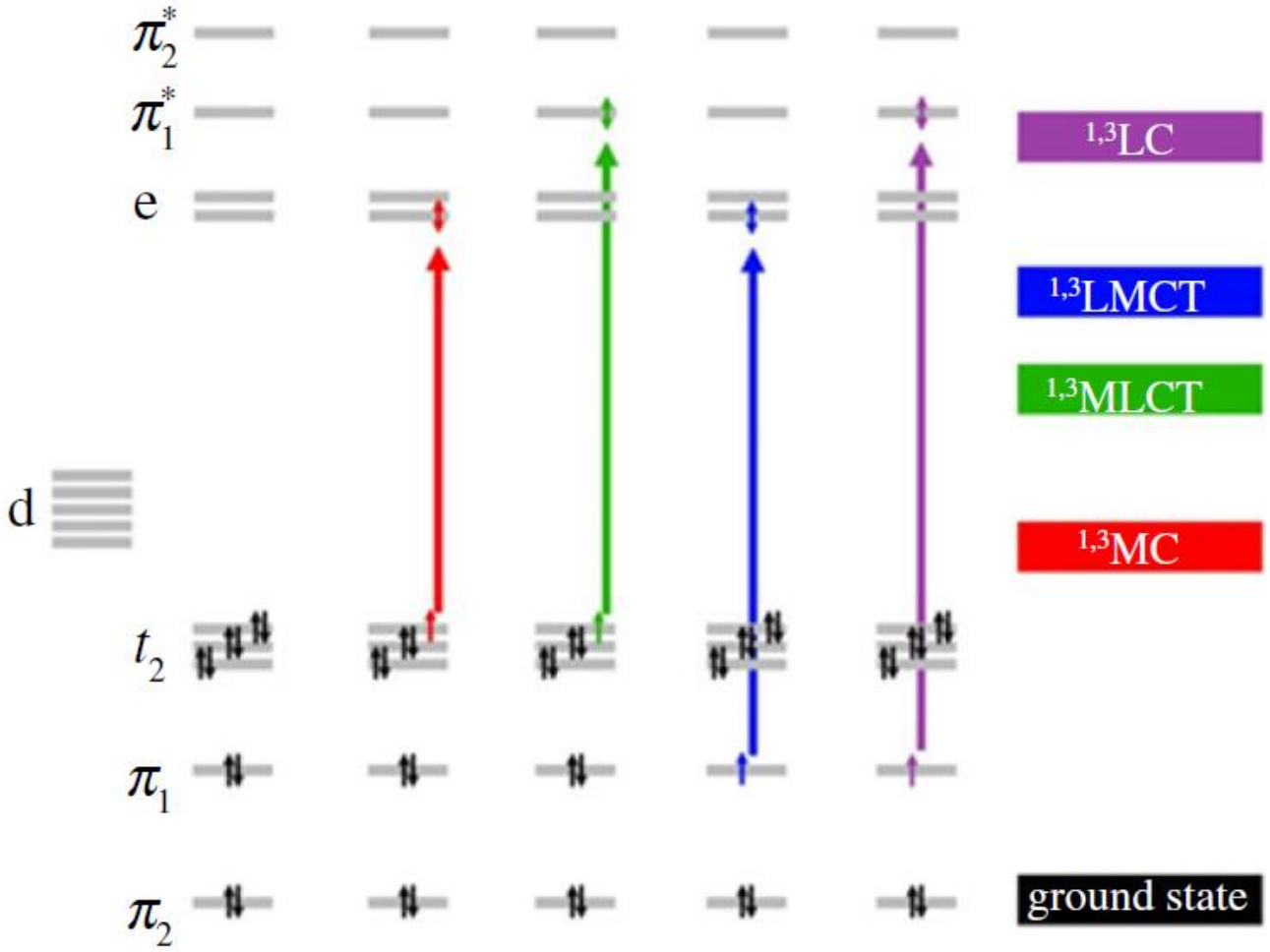
Derivati del BODIPY (*boron-dipyrromethene)*



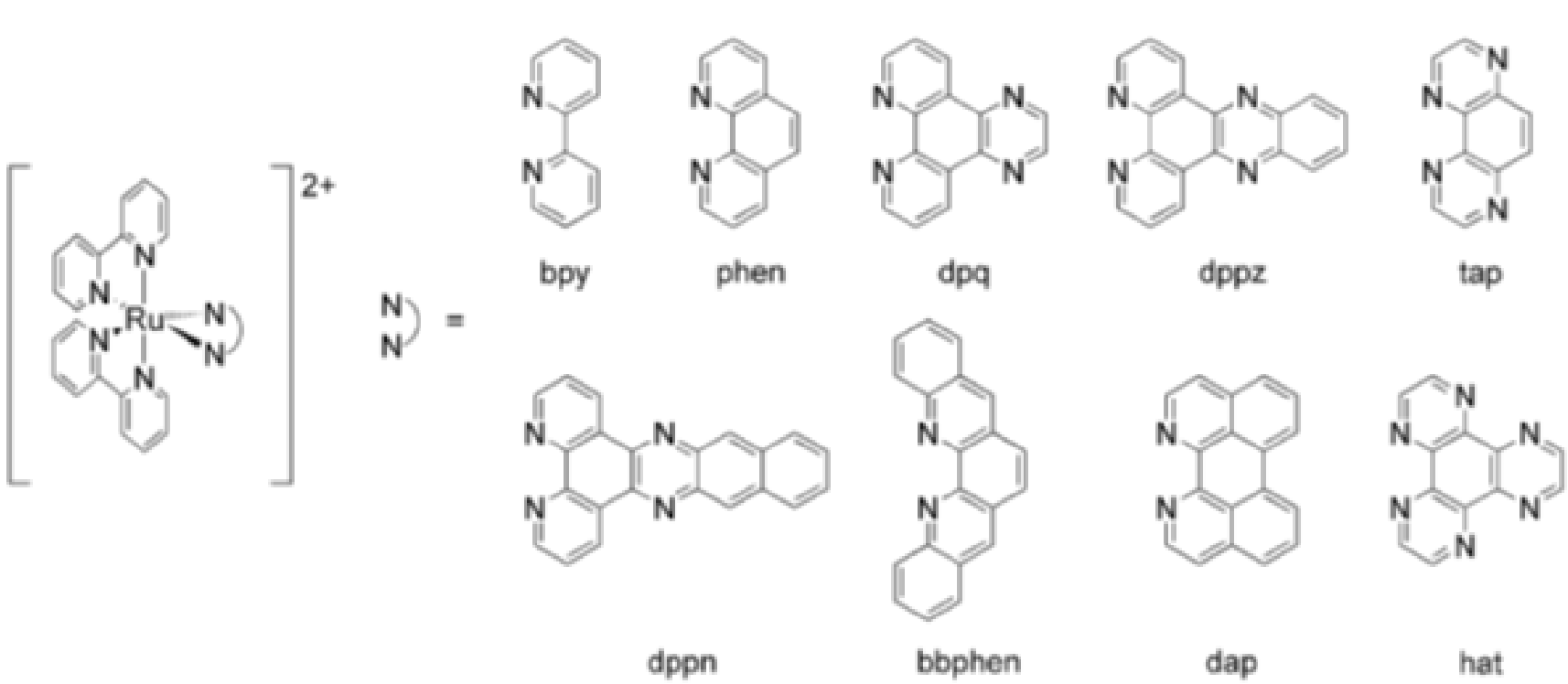




Photoactivatable metal compounds

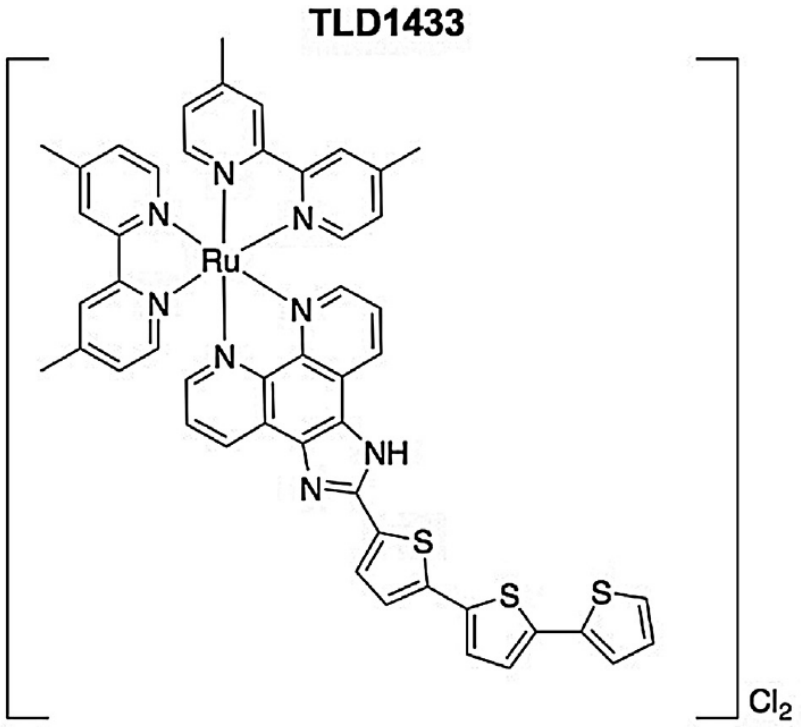


Metal compounds for PDT

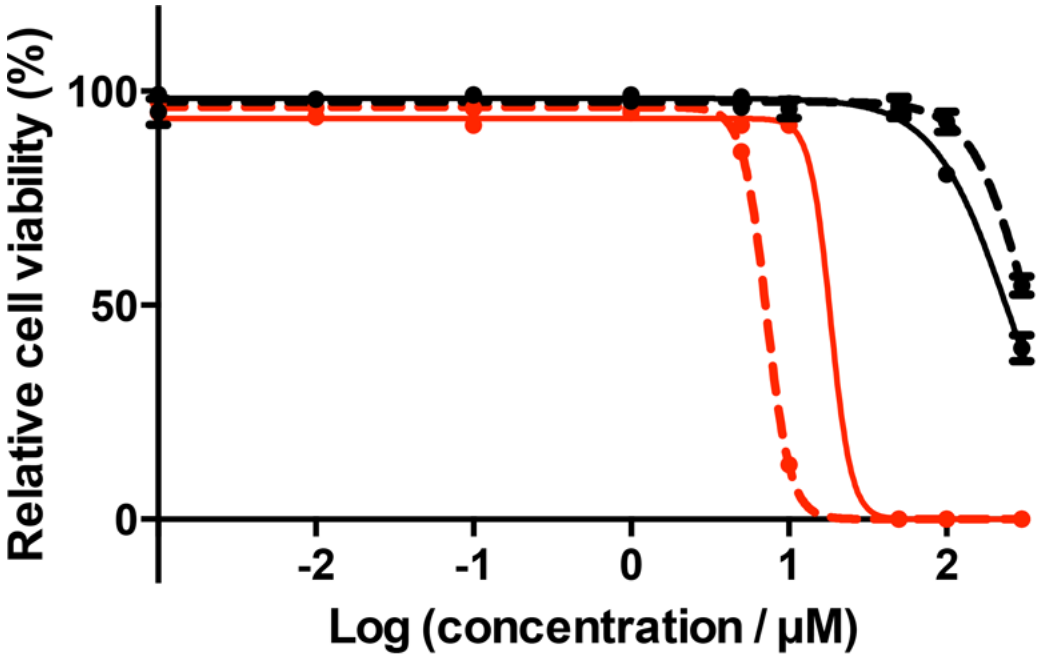


Health Canada Approves Clinical Trial Application for Anti-Cancer Drug

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

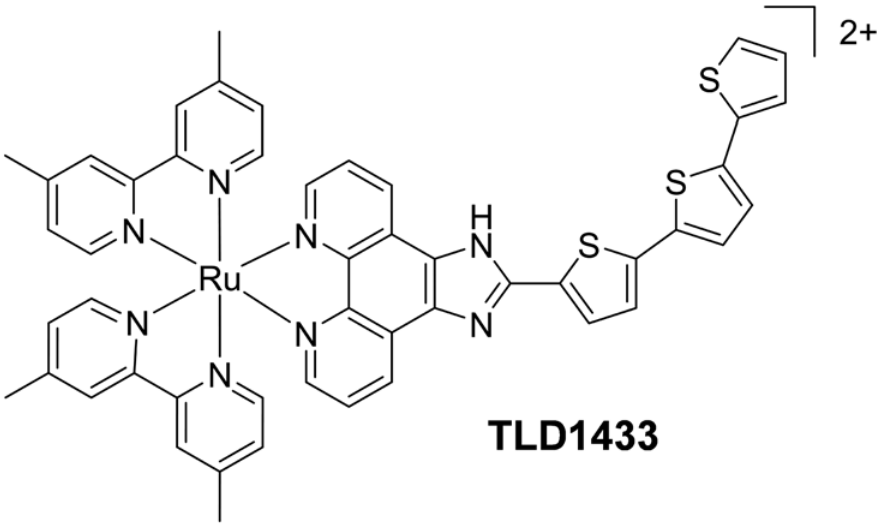


TLD1433, Dark EC_{50} > 300 µM

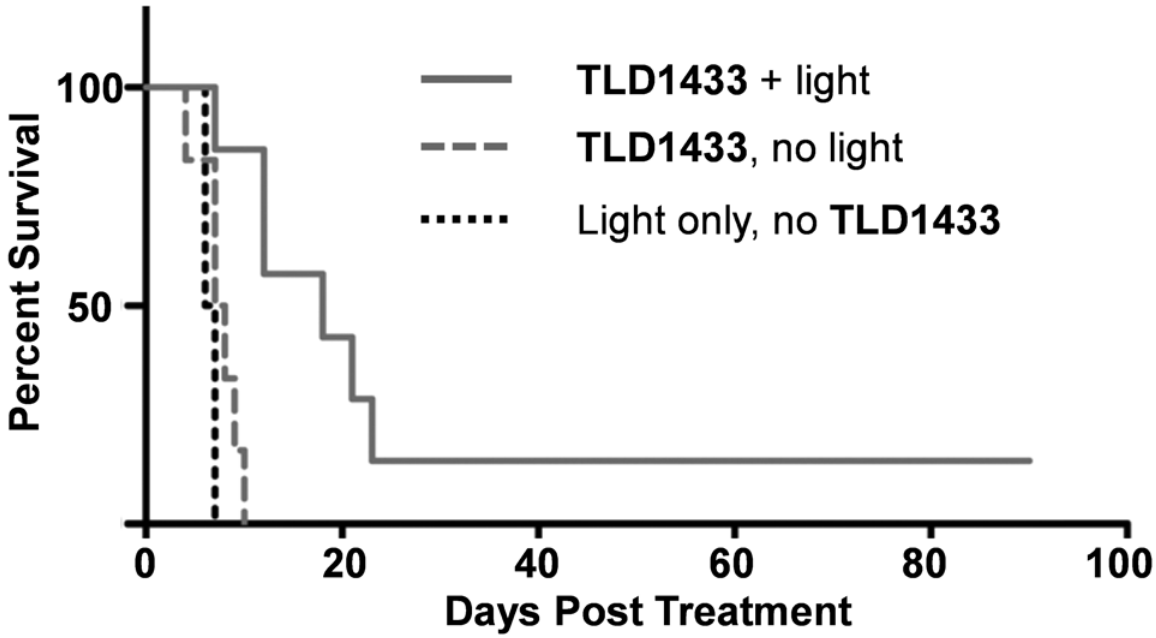
TLD1433, Red EC_{50} = 7.20 ± 1.10 µM

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

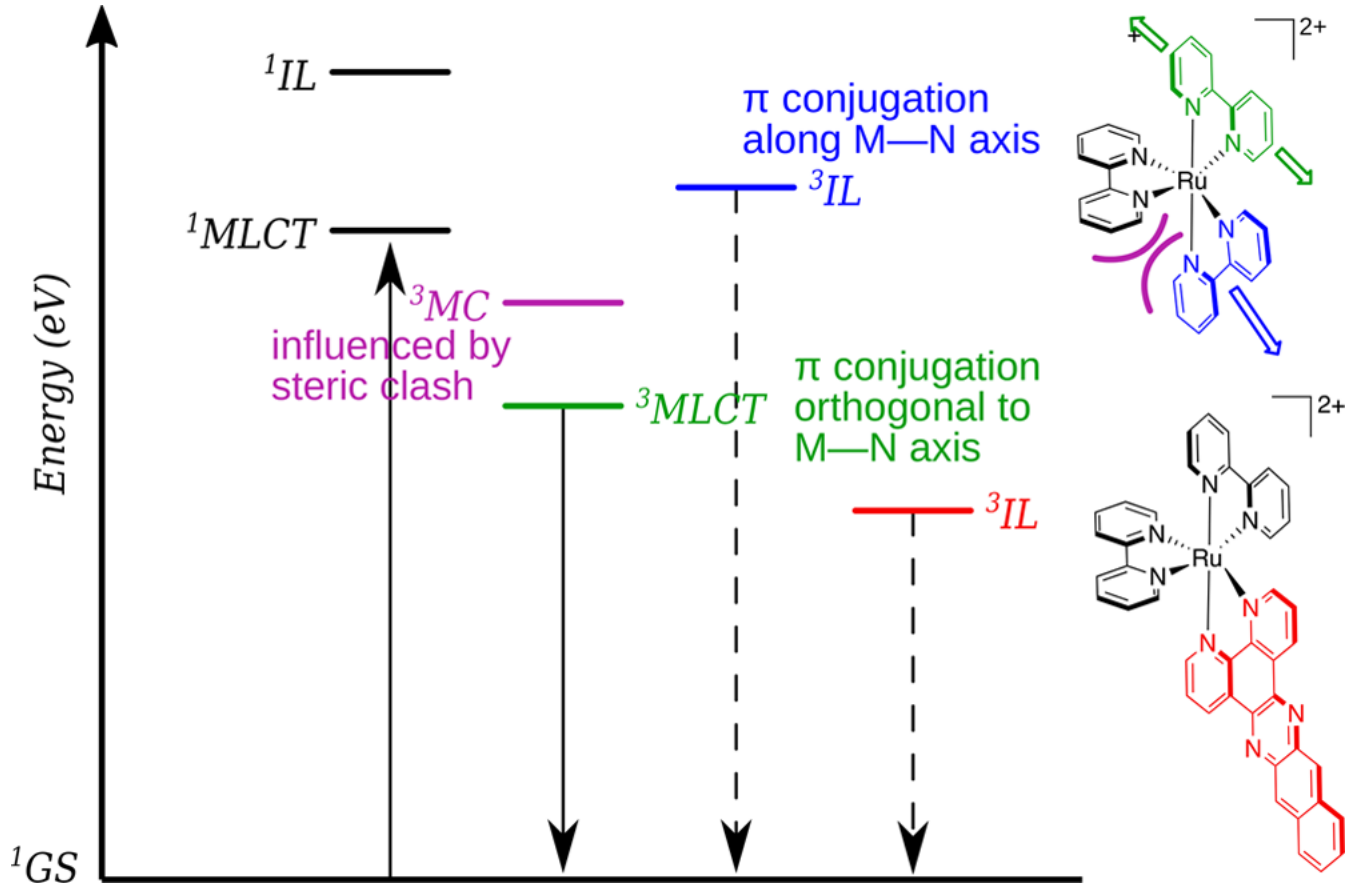
$[Os(dmb)_2(IP\text{-}3T)]Cl_2$, Red EC_{50} = 18.4 ± 0.1 µM


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

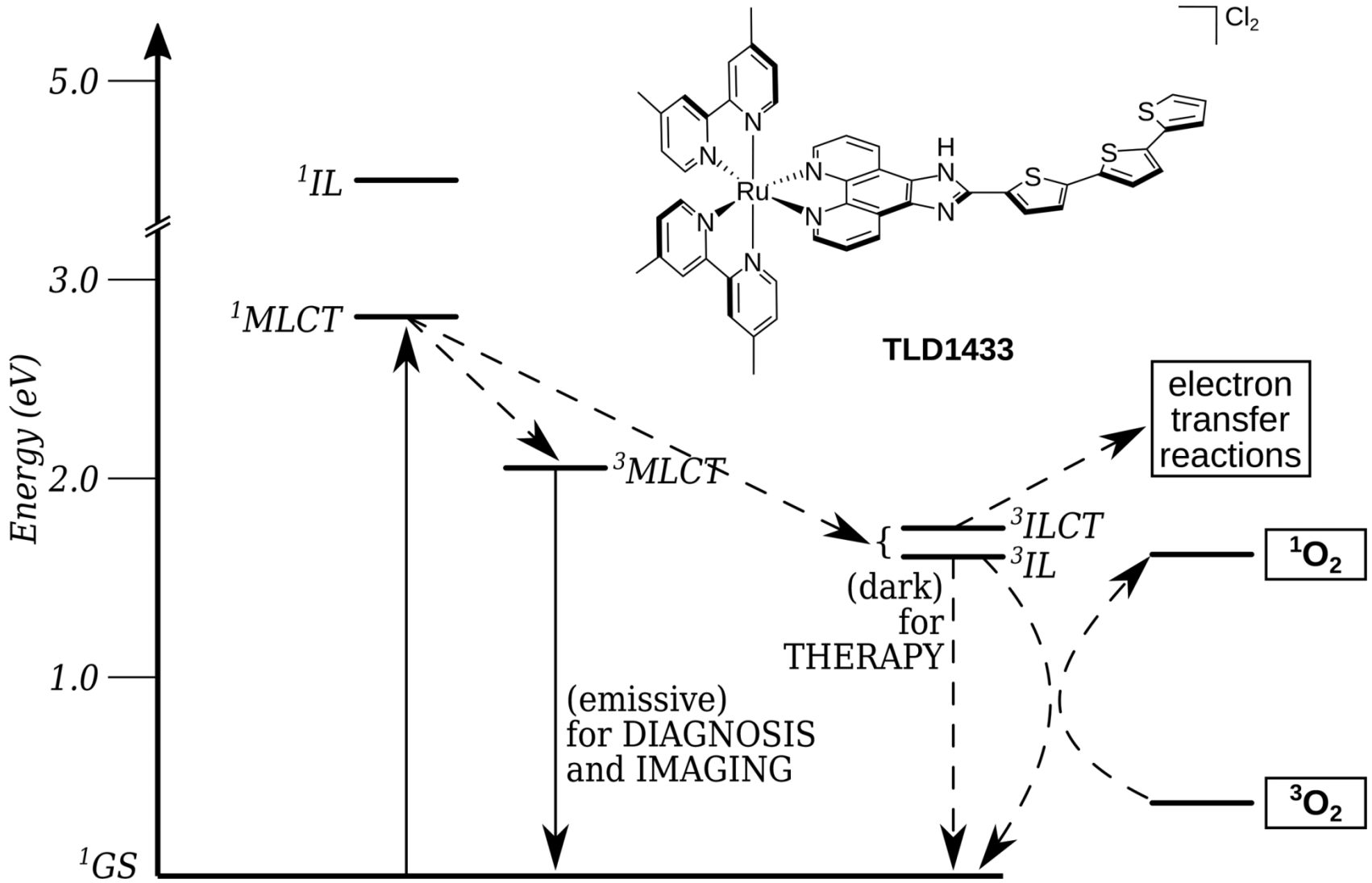
TLD1433


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

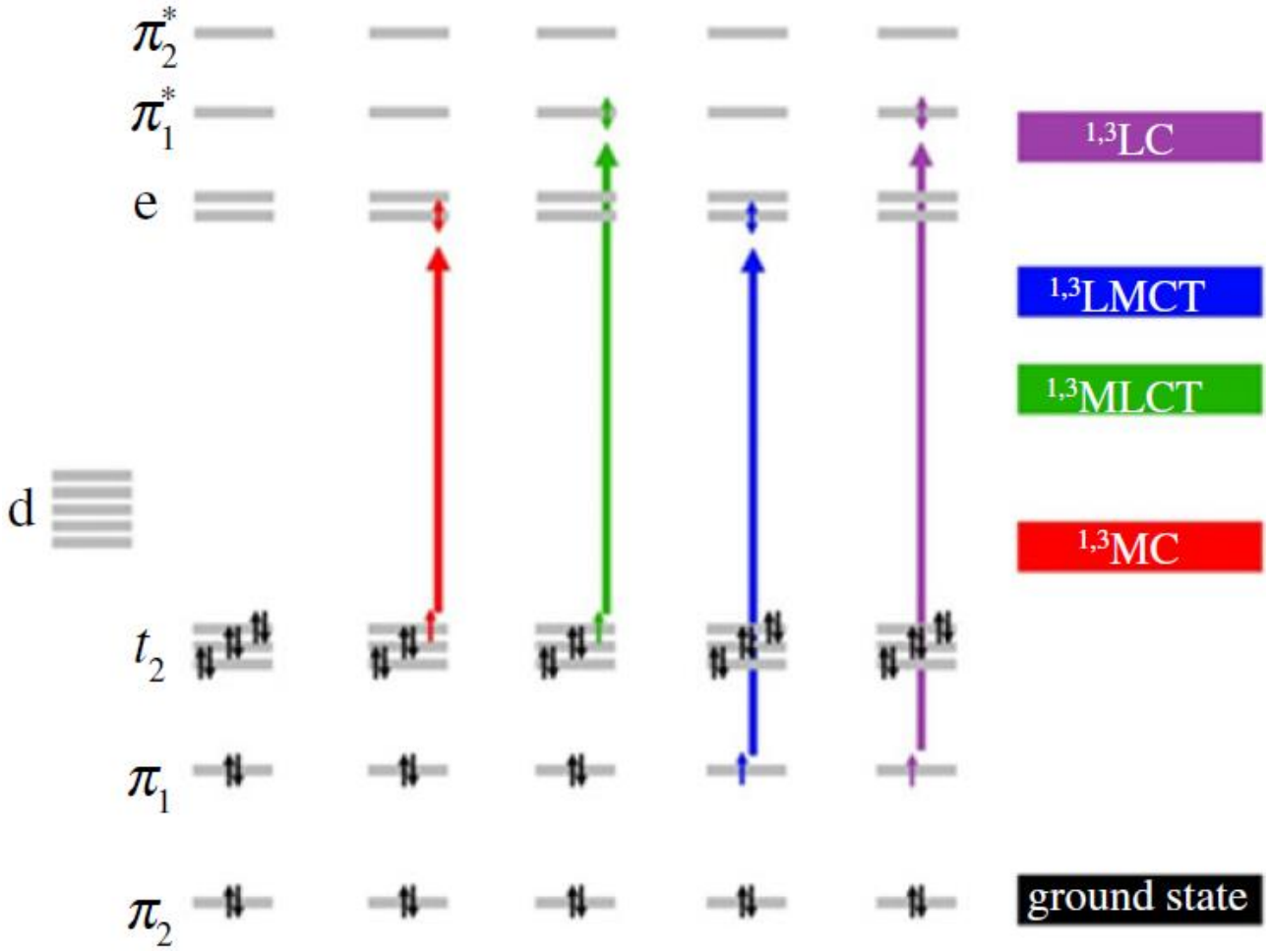
Elementi di design molecolare



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


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

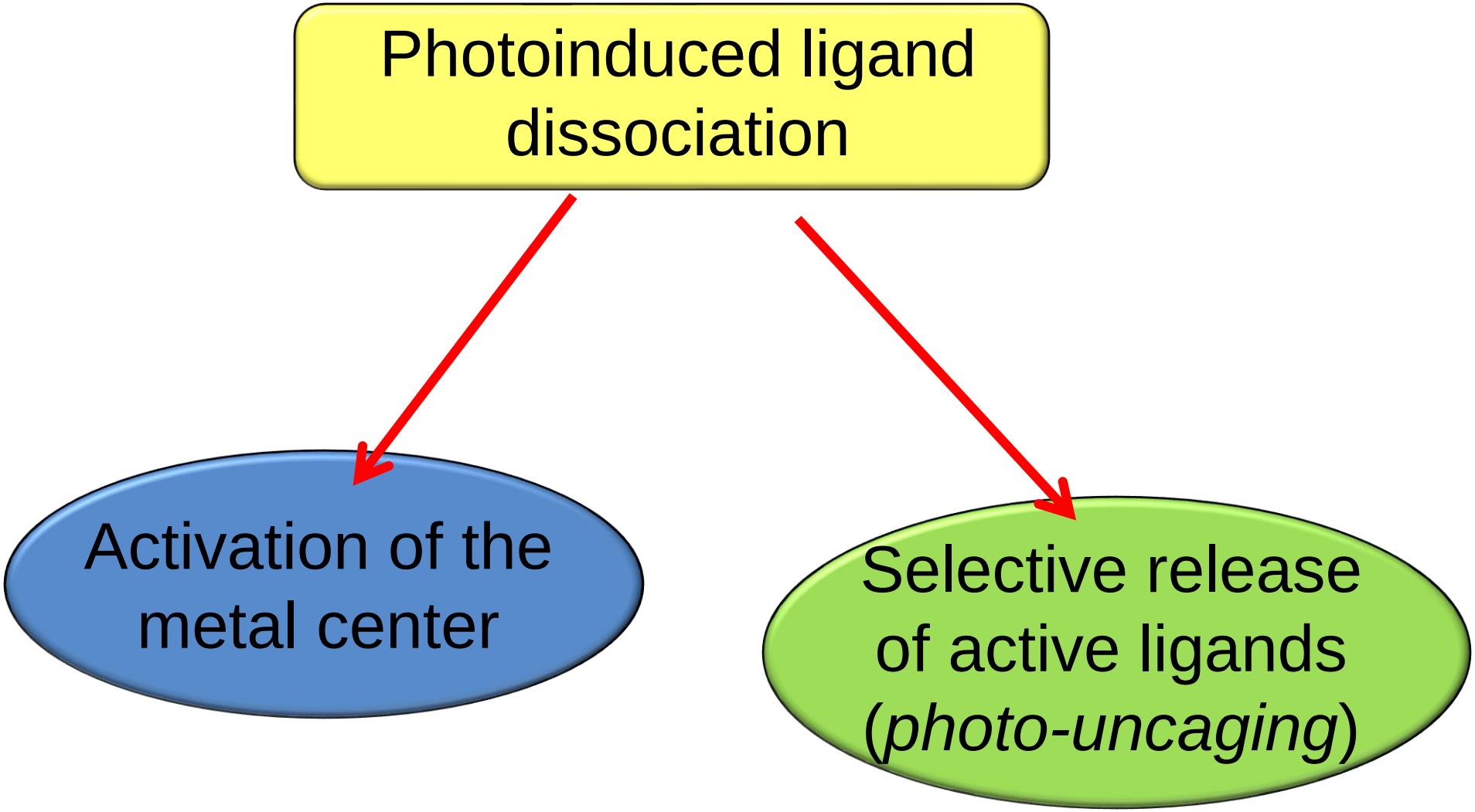
Photoactivatable metal compounds



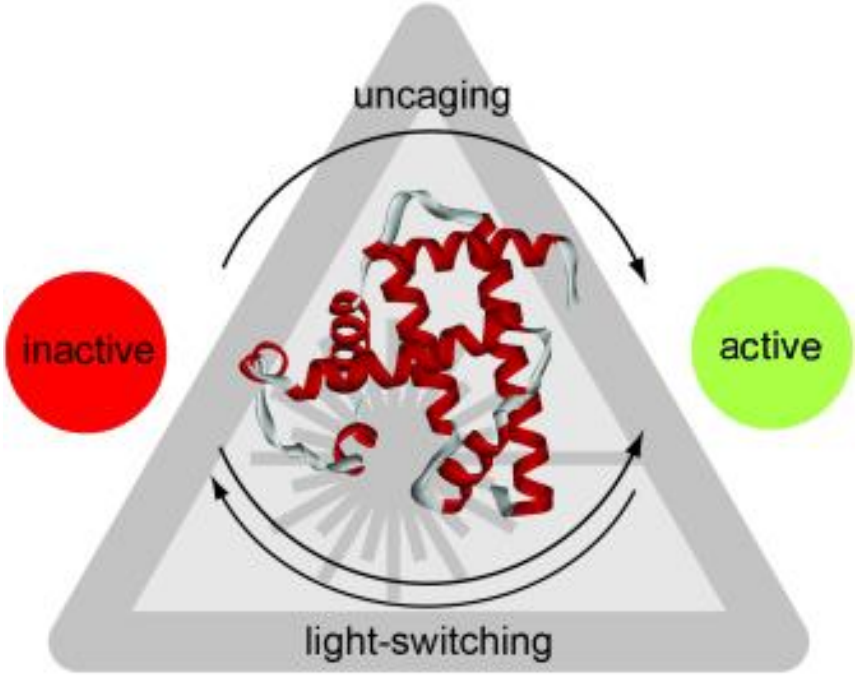
Photoactivatable metal compounds

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.

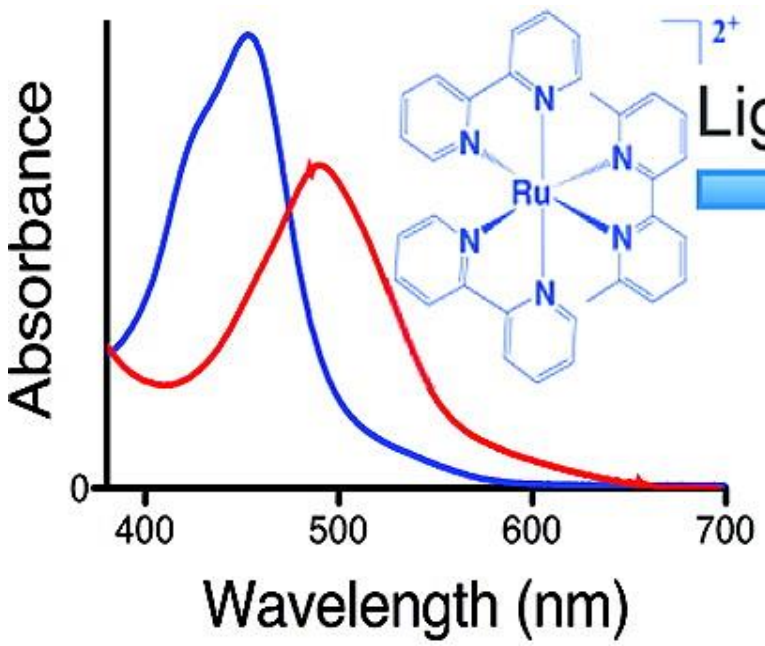

Photoinduced ligand dissociation
Activation of the metal center
Selective release of active ligands (*photo-uncaging*)

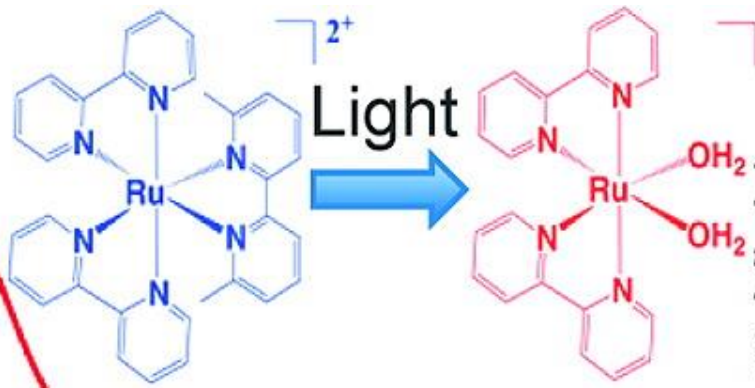
Caged compounds and photo-uncaging

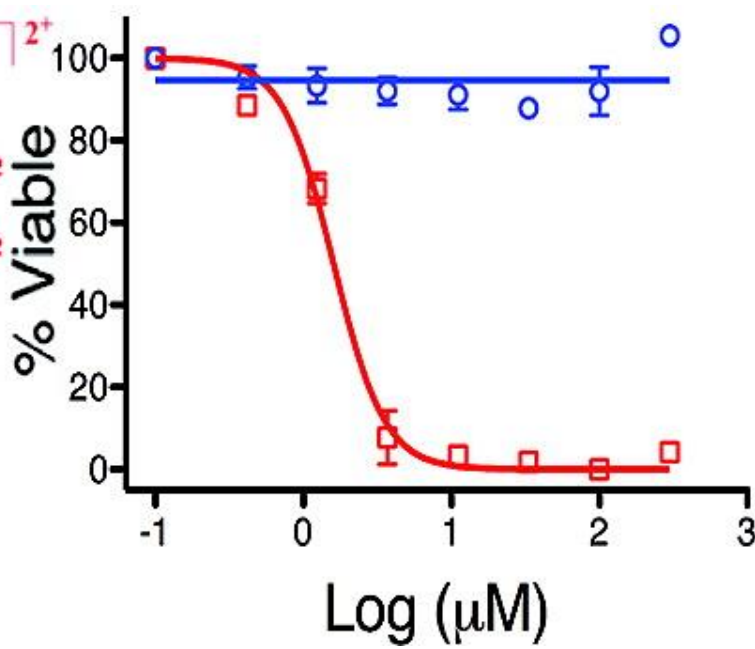


Photolabile protecting groups, attached to a defined position of a molecule, can be used to gain spatio-temporal control over the concentration of the active form of a molecule.

Photoactivatable Ru compounds

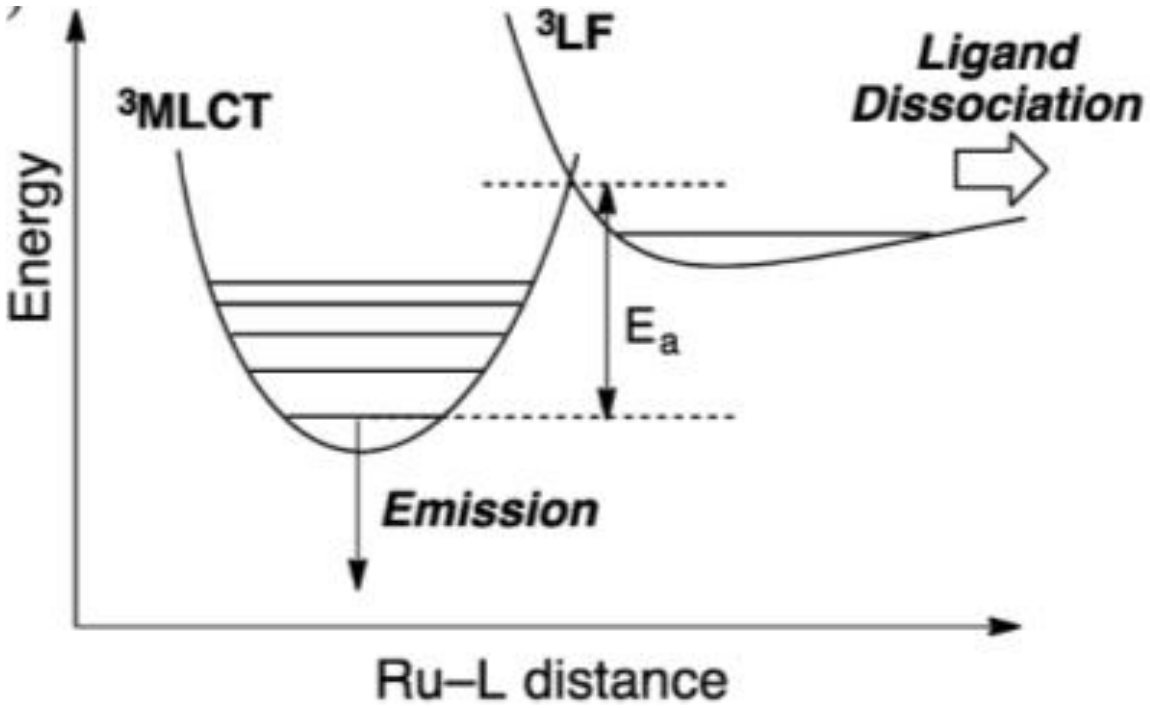


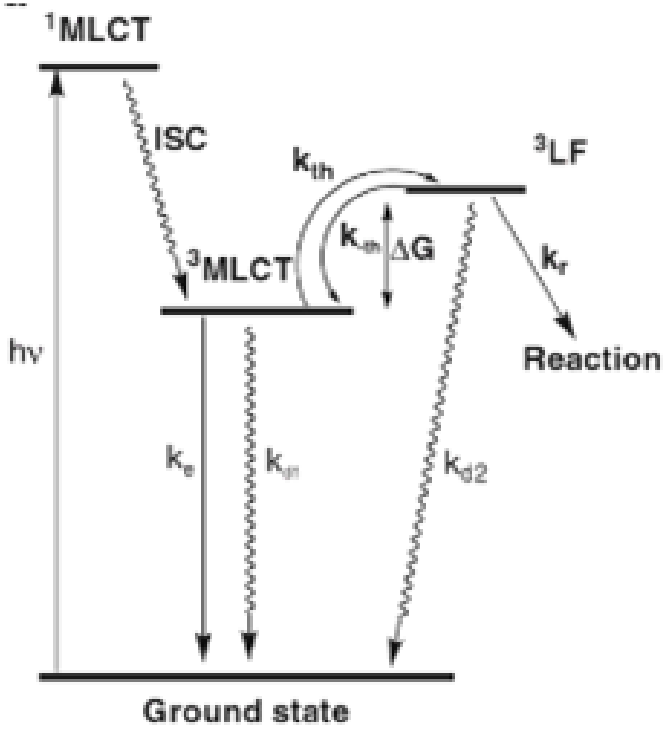


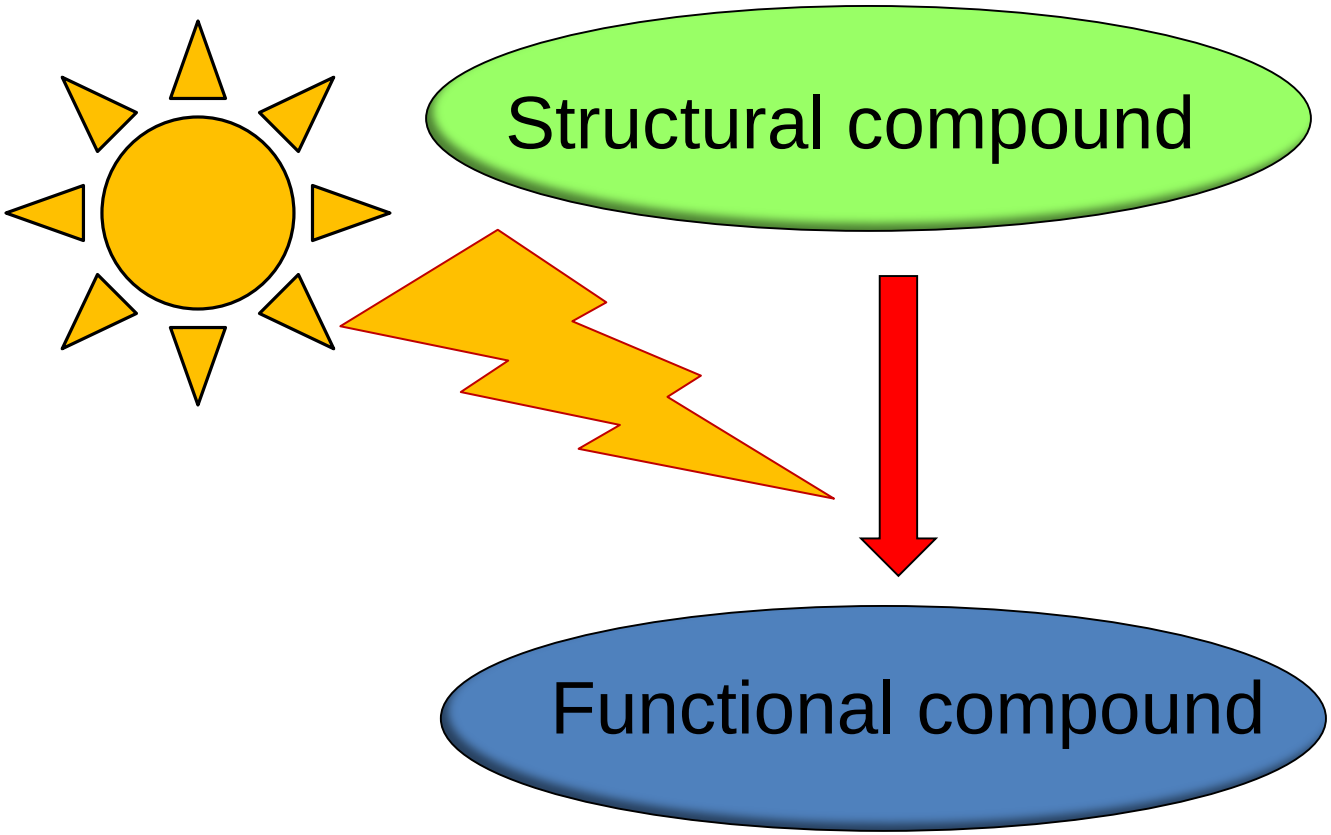


Phototoxicity Index, PI

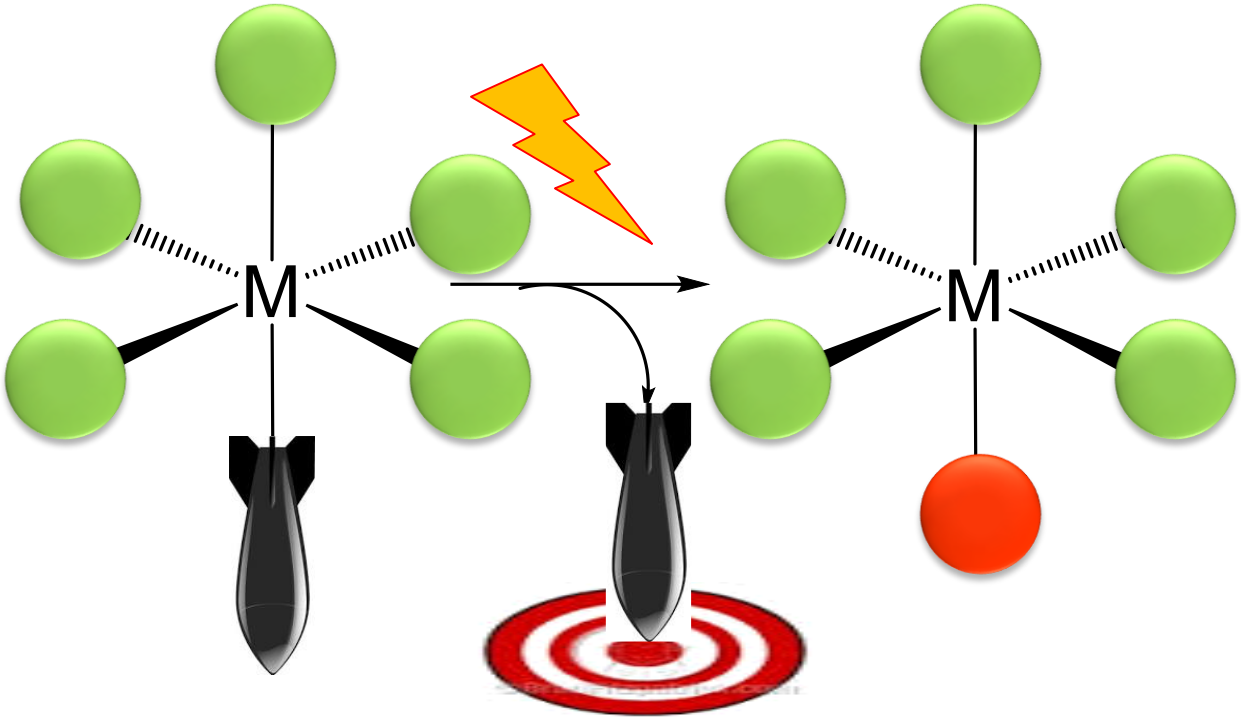
Photoactivatable Ru compounds






Structural compound
Functional compound

Metal compounds for the delivery of active molecules

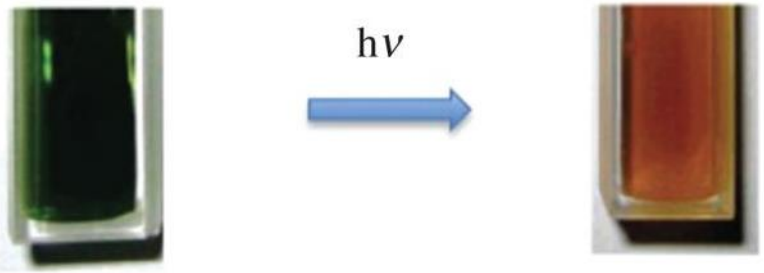


= NO, CO, 4-aminopyridine (4-AP, K^+ channel blocker), γ-aminobutyric acid (GABA, a neurotransmitter),…

Caged compounds and photo-uncaging

NO Releasing Molecules = NORM
CO Releasing Molecules = CORM

Photo-NORM
Photo-CORM



$[Mn(PaPy_3)(NO)]^+$ $[Mn(PaPy_3)(H_2O)]^+$

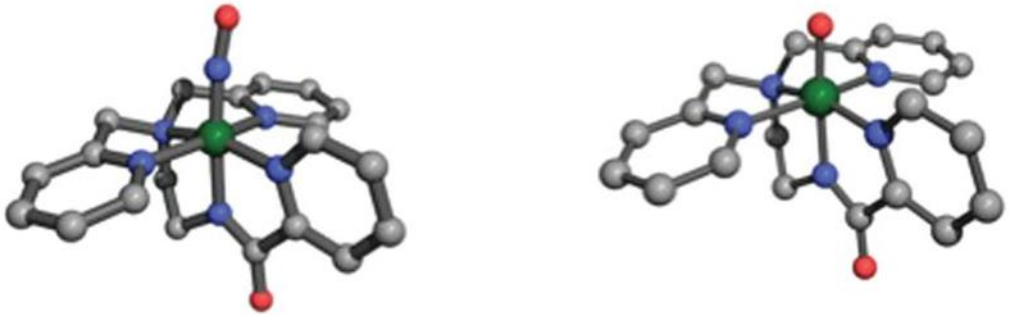
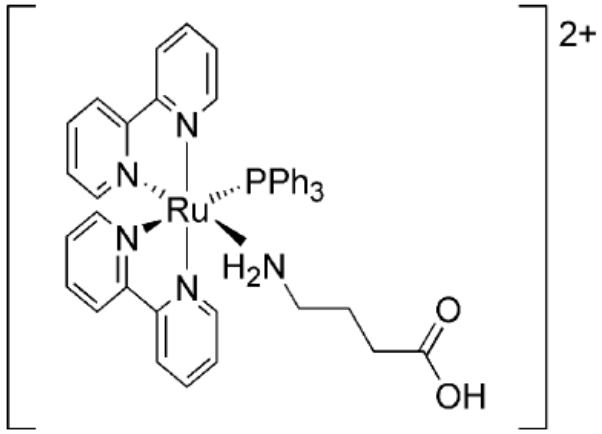
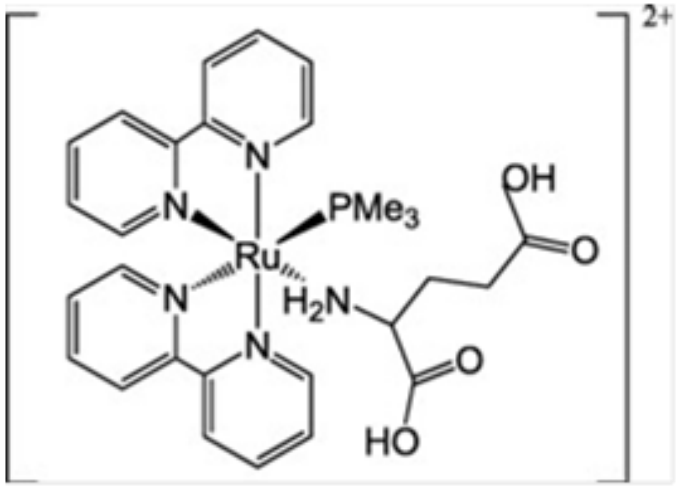
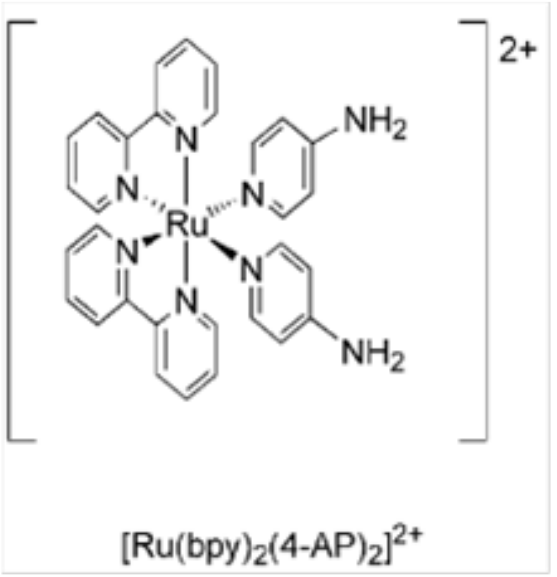


Photo-release of neurotransmitters



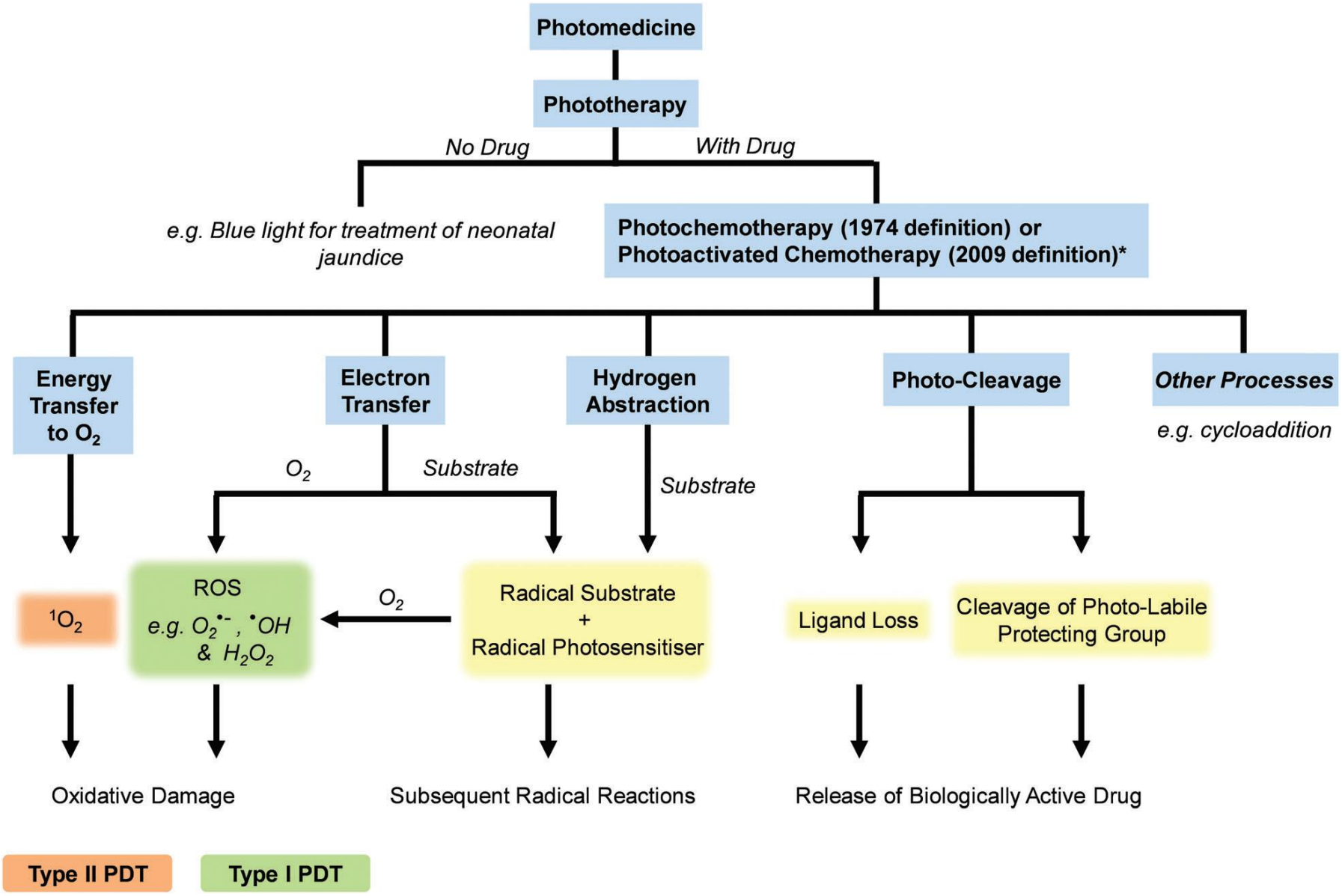
$[Ru(bpy)_2(PPh_3)(GABA)]^{2+}$





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

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