MECHANISTIC DECODING OF TARGET PHOTOTOXICITY: A COMPUTATIONAL STUDY POWERED BY ESIGNS

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WAY2DRUG BCADD-2026

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HIGH COST OF LATE-STAGE DRUG DEVELOPMENT FAILURE

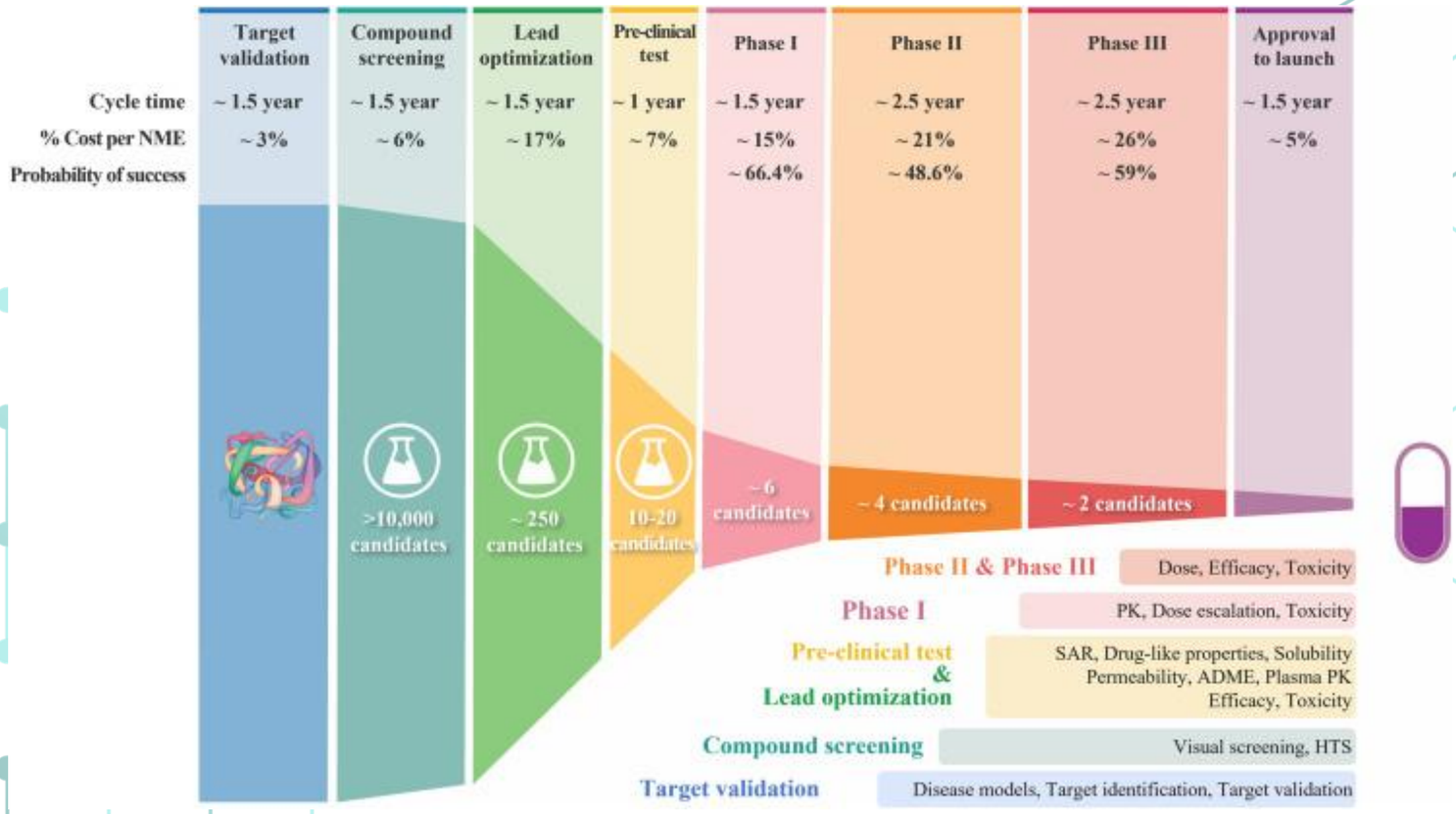


Fig.1 - The process of drug discovery and development, and the failure rate at each step
source https://doi.org/10.1016/j.apsb.2022.02.002

TOXICITY IS A BIG KILLER OF NEW DRUG ENTITIES (~30%)

PHOTOTOXICITY: AN UNDERESTIMATED HAZERD

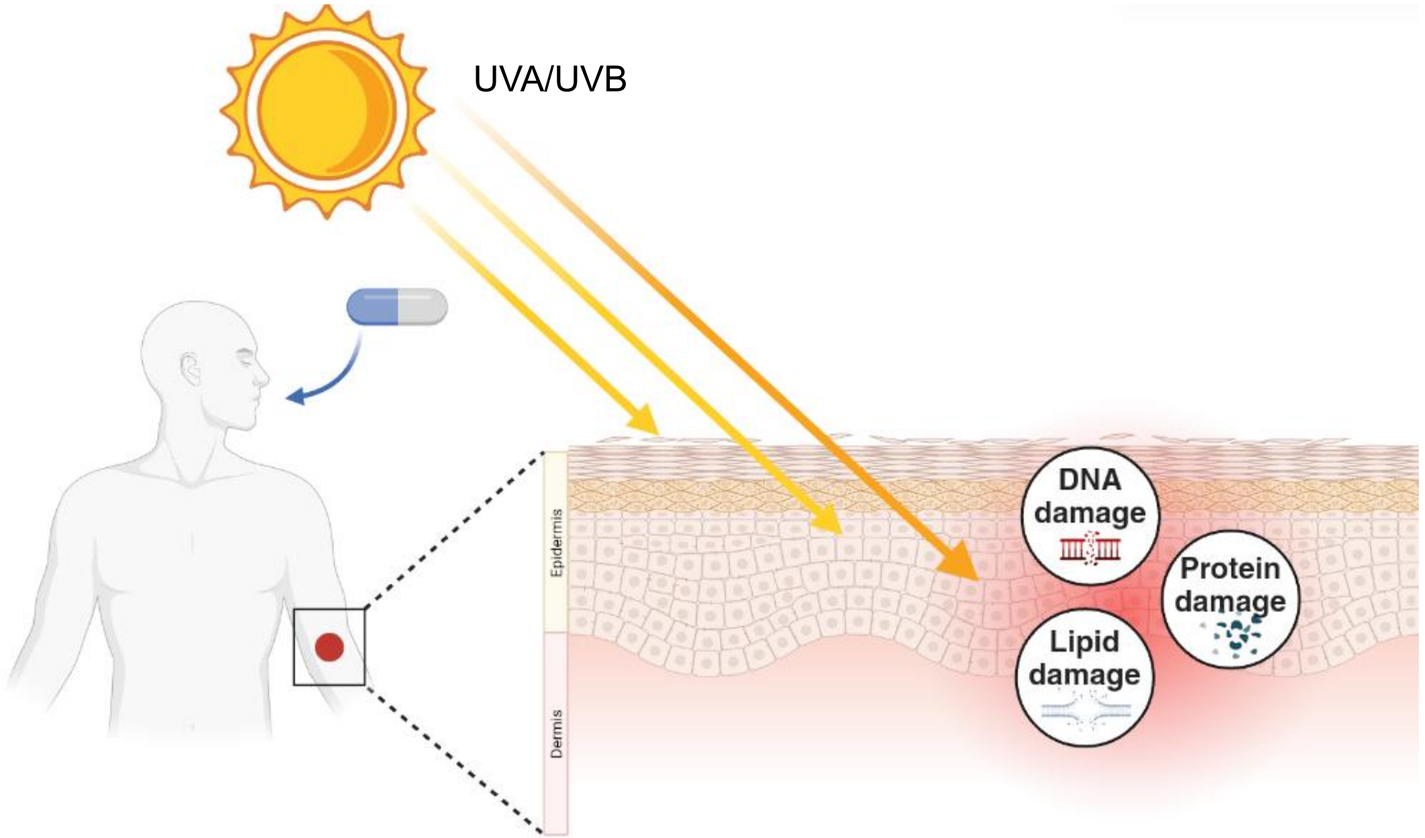
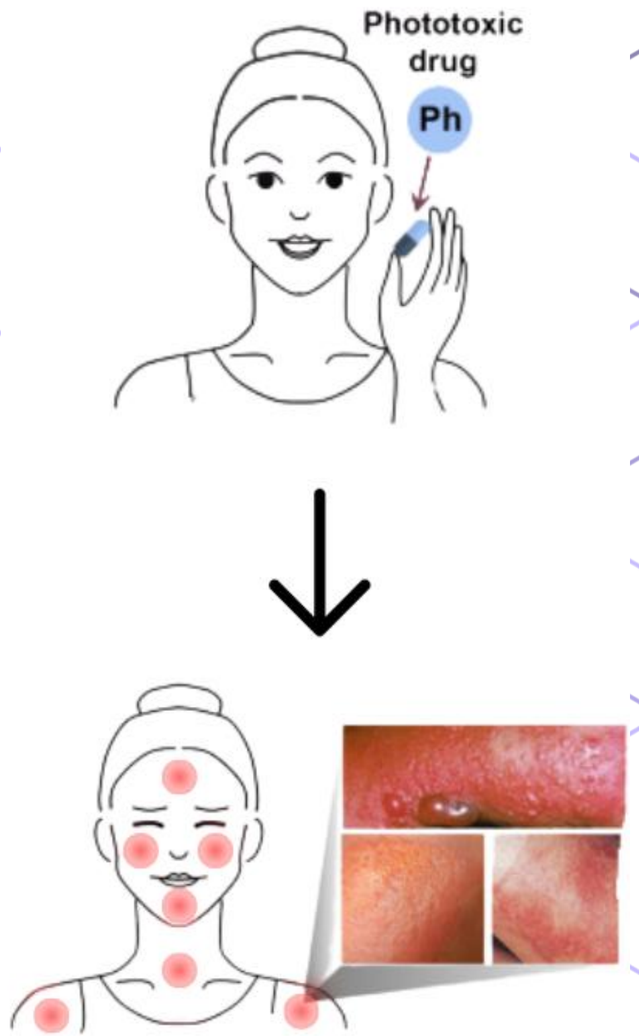


Fig.1 -Drug-induced photosensitivity and light-mediated cellular damage



PHOTOTOXICITY: AN UNDERESTIMATED HAZERD

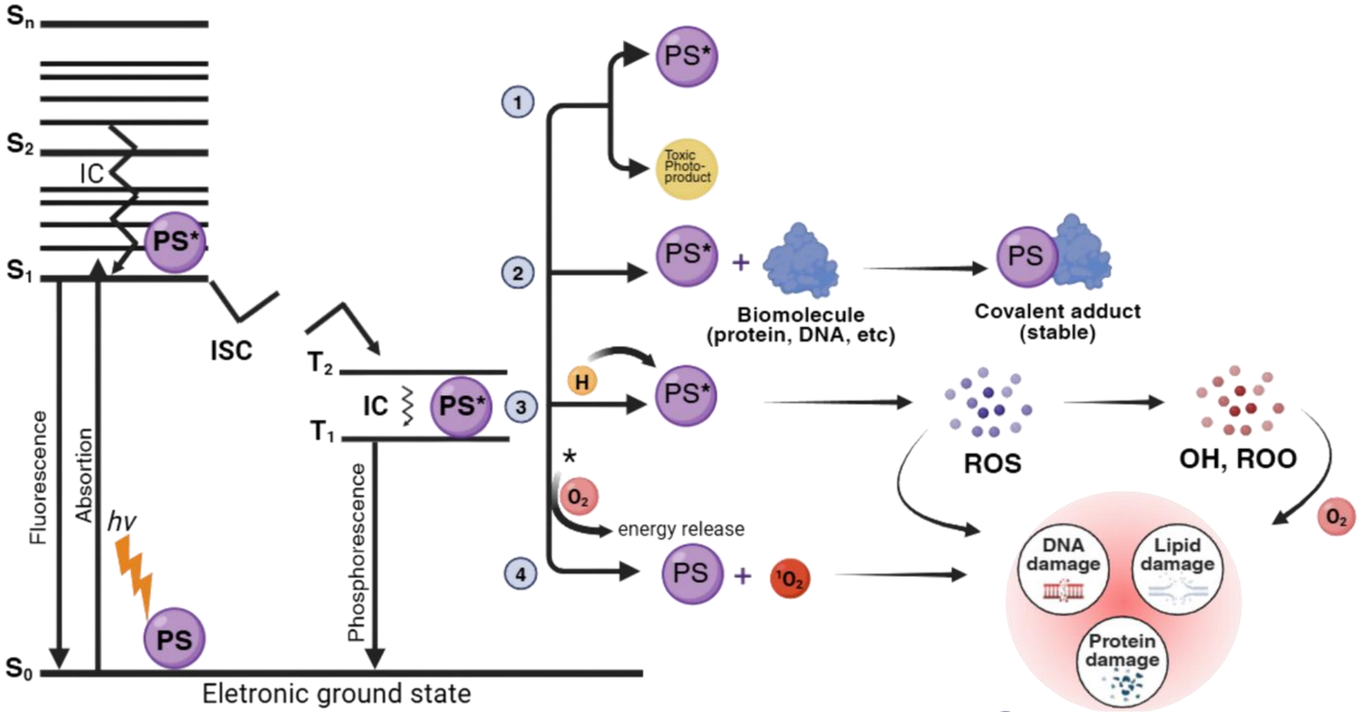
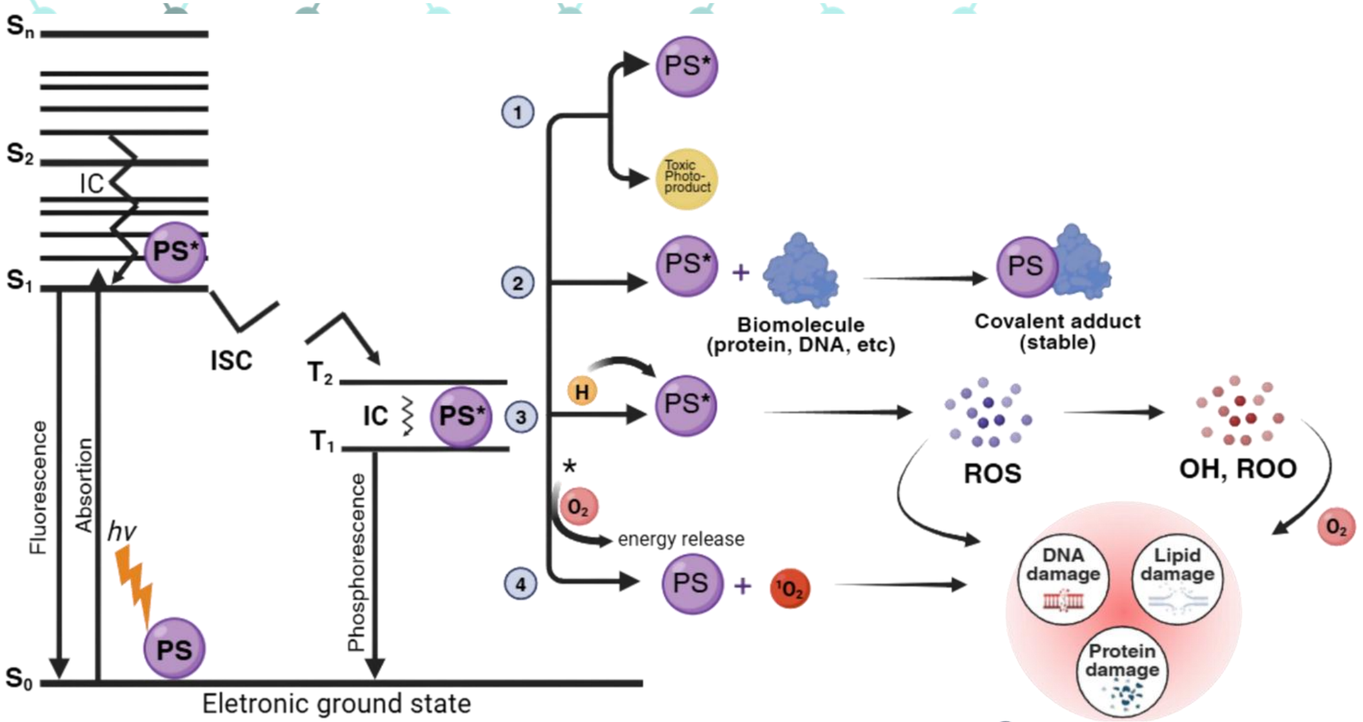




Fig.2 - Excited-State Photophysical Deactivation Channels and Primary Photosensitization Pathways.

WHY TRADICTION PREDICTIVE MODELS FAIL?

TRADITIONAL QSAR MODELS AND STATIC STRUCTURAL ALERTS PRODUCE FALSE NEGATIVES.



Photosensitizing Drug (ground state) PS

Photosensitizing Drug (excited state) PS*

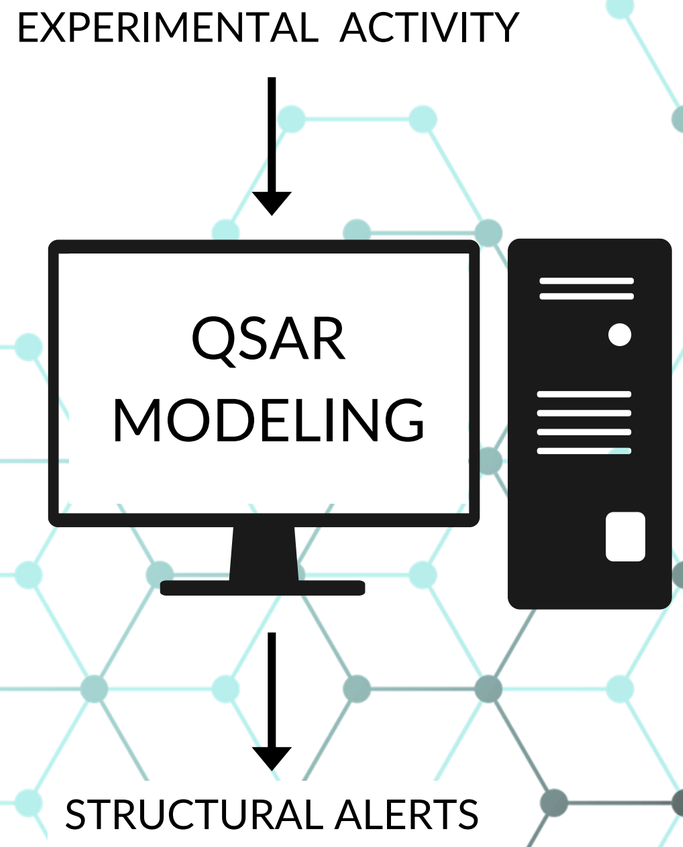
Molecular Oxygen O_2

Hidrogen H

Singlet oxygen $^1O_2$

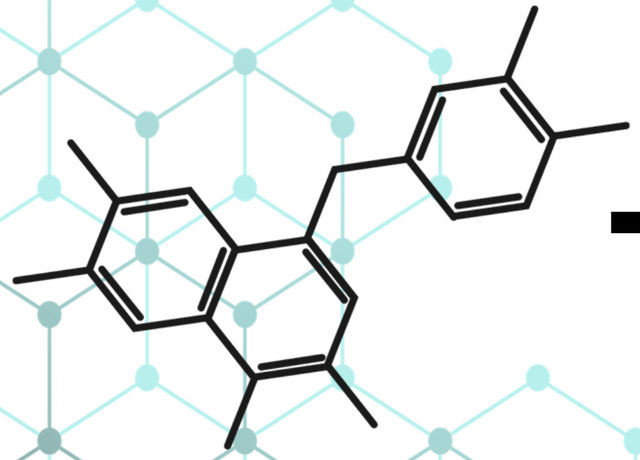
S - Singlet state
T - Triplet state
ISC - Intersystem Crossing
IC - Internal Convertion

Fig.2 - Excited-State Photophysical Deactivation Channels and Primary Photosensitization Pathways.

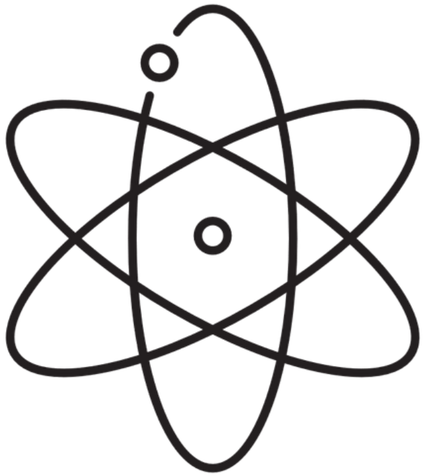


PROJECT GOAL: QUANTUM-DERIVED DESCRIPTORS

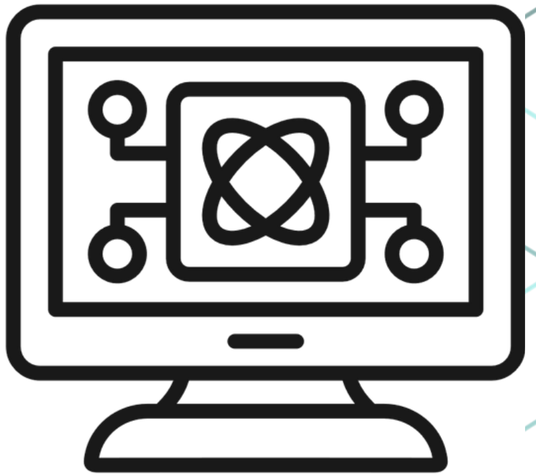
PHOTOTOXIC MOLECULE



QUANTUM-DESCRIPTORS



E-SIGNS

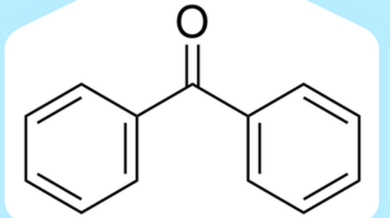


Algorithms grounded in excited-state electronic structure

PHASE 1 - MECHANISTIC MAPPING AND DATASET CURATION

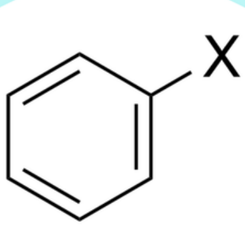
CATEGORIZED 39 BENCHMARK PHOTOSENSITIZING DRUGS
ACROSS FIVE REACTIVE CHROMOPHORE FAMILIES

DIARYL KETONE (BENZOPHENONE-TYPE)



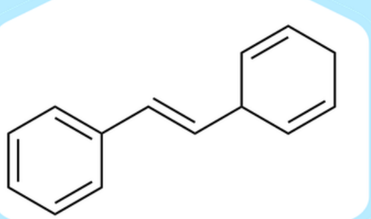
IONISATION-GATED PHOTODECARBOXYLATION; ACCUMULATED PHOTOPRODUCTS SENSITISE ROS MORE EFFICIENTLY THAN PARENT.

HALOGENATED ARYLS



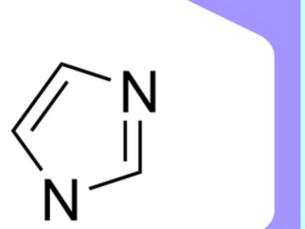
MECHANISTICALLY DIVERSE: OUTCOME RANGES FROM PRIMARY C-X HOMOLYSIS TO COMPLETE HALOGEN INERTNESS.

SUBSTITUTED ALKENES/POLYENES



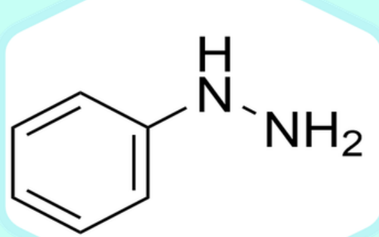
PHOTOISOMERIZATION AND ELECTROCYCLIC RING CLOSURE; PHOTOTOXICITY DELAYED BY INDUCTION PERIOD FOR PHOTOPRODUCT BUILD-UP.

N-RICH HETEROAROMATICS



EFFICIENT ISC TO REACTIVE T_1; DOMINANT TYPE II $^1O_2$ SENSITISATION; MICROENVIRONMENT SHIFTS T_1 ORBITAL CHARACTER AND PATHWAY.

ARYL-AMINE DONOR-ACCEPTOR SYSTEMS



EXCITED-STATE ELECTRON TRANSFER TO RADICAL CATION/IMINIUM; DAMAGE VIA TRANSIENT SPECIES, NOT STABLE PHOTOPRODUCTS.

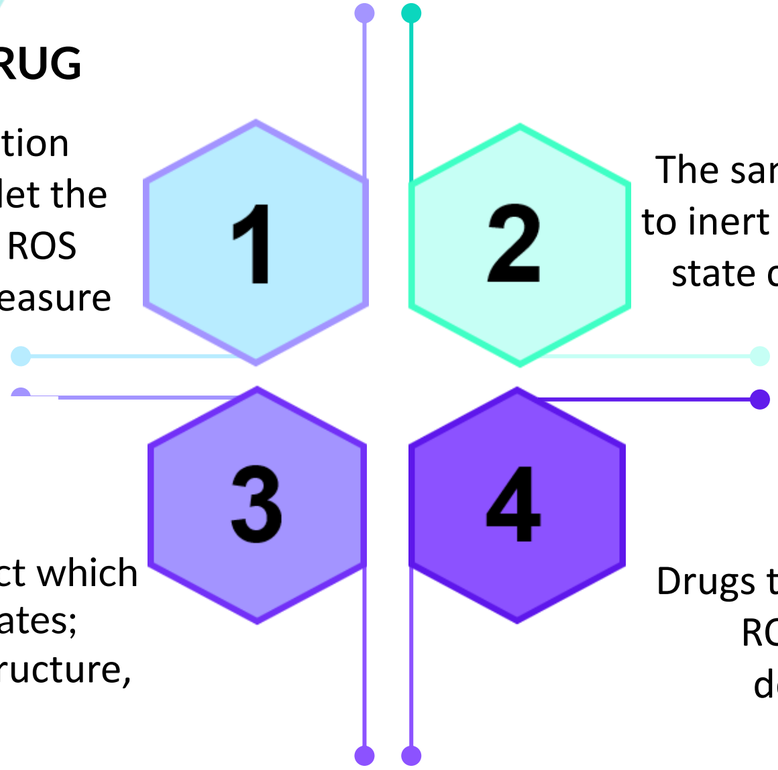
PHASE I INSIGHTS: MECHANISTIC PRINCIPLES

PHOTOTOXIC AGENT ≠ PARENT DRUG

Photoproducts lose a protective deactivation channel, gain conjugation, or acquire a triplet the parent lacks, becoming far more efficient ROS sensitisers; parent-disappearance assays measure the wrong species.

MICROENVIRONMENT OVERRIDES SCAFFOLD

Protein binding, pH, and oxygen tension select which excited-state deactivation channel dominates; Excited-state behaviour, not ground-state structure, is the decisive gate.



STRUCTURAL ALERTS ARE CONTEXT-DEPENDENT

The same aryl halogen spans primary reactive site to inert spectator depending on competing excited-state channels; the bond’s environment, not the halogen itself, decides

PHOTOSTABILITY DOES NOT EQUAL PHOTOSAFETY

Drugs that survive irradiation intact can sensitise ROS catalytically; an unchanged parent demonstrates persistence, not safety.

PROJECT WORKFLOW

PHASE I

MECHANISTIC MAPPING & DATASET CURATION

SYSTEMATIC CATEGORIZATION OF PHOTOTOSINSITEZER DRUGS ACROSS REACTIVE CHROMOPHORE FAMILIES

PHASE II

INTERMOLECULAR INTERACTION POTENTIAL

ANALYSIS OF NON-COVALENT PERTURBATIONS AND MOLECULAR DOCKING

PHASE III

ESIGNS FINGERPRINT ENCODING

DERIVING SYSTEMATIC DESCRIPTORS FROM ELECTRONIC PROPERTIES (ISC, TRIPLET ENERGIES)

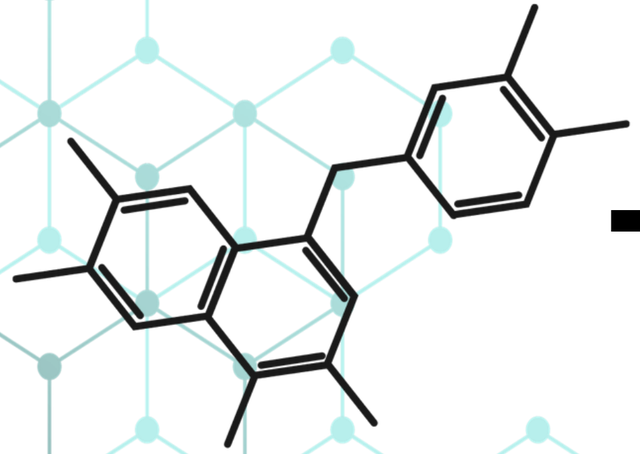
PHASE IV

AI ASSESSMENT & QSAR VALIDATION

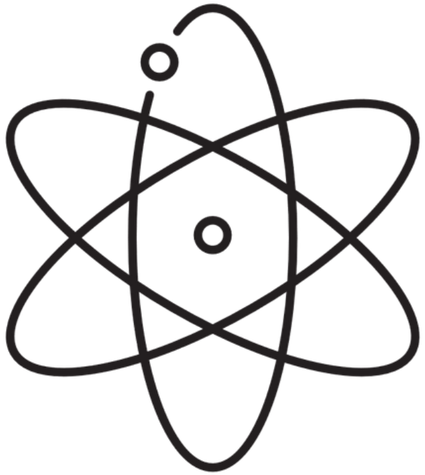
DEPLOYMENT OF AI ENGINE TO COMPARE ESIGN PERFORMANCE AGAINST TRADITIONAL MODELS

TAKE HOME MESSAGE

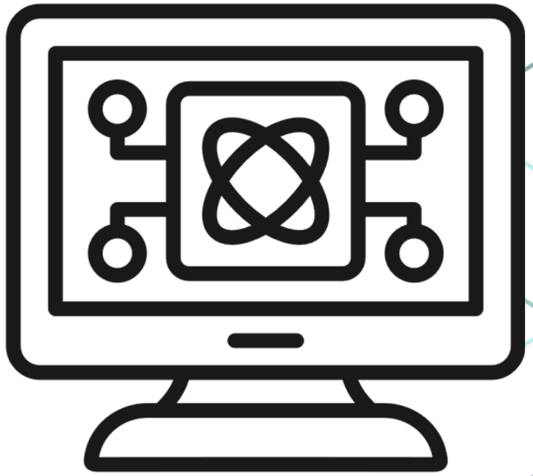
PHOTOTOXIC MOLECULE



QUANTUM-DESCRIPTORS



E-SIGNS



THE PRIMARY BOTTLENECK IN PREDICTIVE PHOTOTOXICITY IS NOT ABSENT PHYSICAL UNDERSTANDING BUT THE LACK OF A SCALABLE IMPLEMENTATION THAT RETAINS MECHANISTIC FIDELITY ALL THE WAY TO THE TOXICOLOGICAL ENDPOINT.

MECHANISTIC DECODING OF TARGET PHOTOTOXICITY: A COMPUTATIONAL STUDY POWERED BY ESIGNS

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[1]LAQV REQUIMTE, Chemistry Department, NOVA School of Science and Technology | NOVA FCT, Portugal
[2]FastCompChem, Portugal

Why study phototoxicity?

Over 400 distinct photosensitizing compounds identified trigger severe cutaneous photoallergy, photohemolysis, and long-term risks of skin malignancies that causes patient hospitalizations, therapy discontinuation, and costly late-stage pharmaceutical attrition.

Why Current Screening Fails?

- Current regulatory assays (ICH10, ICH Q1B) record whether photochemistry occurs and not why;
- Traditional QSARs and structural alerts ignore excited-state dynamics like intersystem crossing (ISC), spin-orbit coupling, and triplet lifetimes;
- *In vivo* cell assays assays fail to capture photogenotoxicity and metabolic bioactivation, missing photostable catalytic sensitizers (Photostability ≠ Photosafety).

To address these limitations, we explore whether quantum-chemical descriptors of excited-state dynamics can extend electronic structure fingerprints – Esigns, developed within the QUANTUM-TOX project) – to support mechanism-grounded modeling of drug-induced phototoxicity.

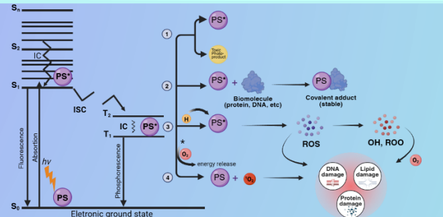


Figure 1. Excited-State Photophysical Deactivation Channels and Primary Photosensitization Pathways.

PhD PROJECT WORKFLOW

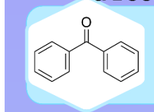
PHASE I
Mechanistic Mapping & Dataset Curation
Systematic categorization of phototosinsitezer drugs across reactive chromophore families.

PHASE II
Intermolecular Interaction Potential
Analysis of non-covalent perturbations and molecular docking.

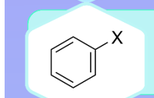
PHASE III
Esigns Fingerprint Encoding
Deriving systematic descriptors from electronic properties (ISC, triplet energies)

PHASE IV
AI Assessment & QSAR Validation
Deployment of AI engine to compare ESign performance against traditional models.

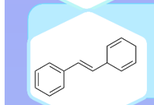
MOIETY-BASED PHOTOREACTIVE CLASSES & BOUNDARY CASES (CURRENT STATE)



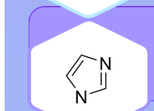
Diaryl Ketone (Benzophenone-type)
Ionisation-gated photodecarboxylation;
Accumulated photoproducts sensitise ROS more efficiently than parent.



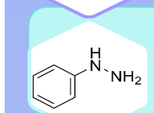
Halogenated Aryls
Mechanistically diverse: outcome ranges from primary C-X homolysis to complete halogen inertness.



Substituted Alkenes/Polyenes
Photoisomerization and electrocyclic ring closure;
Phototoxicity delayed by induction period for photoproduct build-up.



***N*-Rich Heteroaromatics**
Efficient ISC to reactive T_1;
Dominant Type II $^1O_2$ sensitisation; Microenvironment shifts T_1 orbital character and pathway.



Aryl-Amine Donor-Acceptor Systems
Excited-state electron transfer to radical cation/iminium;
Damage via transient species, not stable photoproducts.

Photostable Catalytic Sensitizer
Remains structurally intact yet repeatedly generates $^1O_2$.

External Matrix Systems
Degrades via interaction with matrix excipients or environmental co-solvents.

Uncharacterized / Biologics
Photoproducts detected but unassigned;
No discrete chromophore;

CROSS-CLASS MECHANISTIC PRINCIPLES

1. **Phototoxic agent ≠ parent drug**
Photoproducts retain the core chromophore but lose protective non-radiative deactivation, becoming far more efficient ROS sensitisers;
Parent-disappearance assays systematically fail.
2. **Structural alerts are necessary but insufficient**
The same aryl halogen spans primary reactive site to inert spectator depending on competing excited-state channels; electronic context, not connectivity, decides.
3. **Microenvironment overrides scaffold**
Protein binding, pH, and oxygen tension select which excited-state deactivation channel dominates
ISC orbital character (n,π* vs. π,π*) is the decisive gate, not ground-state structure.
4. **Photostability does not equal photosafety** Uncharacterized pathways do not reflect a lack of physical theory, but rather show that different experimental interventions (e.g., solid-state topochemistry, ROS detection, matrix/co-solvent controls) are required for distinct drug classes.

TAKE-HOME MESSAGE

The primary bottleneck in predictive phototoxicity is not absent physical understanding but the lack of a scalable implementation that retains mechanistic fidelity all the way to the toxicological endpoint.

REFERENCES

[1] Hofmann&Weber, *J. Dtsch. Dermatol. Ges.* **2021**, *19*, 19-29.
[2] Schmidt et al., Computational Investigation of Drug Phototoxicity: Photosafety Assessment, Photo-Toxophore Identification, and Machine Learning. *CHEMICAL RESEARCH IN TOXICOLOGY* **2019**, *32* (11), 2338-2352.
[3] Publications Office of the European Union. QUANTUM-TOX - Revolutionizing Computational Toxicology with Electronic Structure Descriptors and Artificial Intelligence; 2024.

ACKNOWLEDGEMENTS

Fundação para a Ciência e Tecnologia (FCT), I.P., under the scope of the projects UID/50006/2025, UID/PRR/50006/2025, UID/PRR2/50006/2025 and LA/P/0008/2020 of the Associated Laboratory for Green Chemistry - LAQV REQUIMTE. Ana Sofia Almeida acknowledges FCT, I.P., for her doctoral scholarship (2025.05070.BDANA). This work is developed within the Doctoral Program in Sustainable Chemistry at NOVA FCT, in collaboration with FastCompChem.