XXVIII Symposium on Bioinformatics and

Computer-Aided Drug Discovery

IBMC
Institute of Biomedical Chemistry

QSPR Analysis in Photonics

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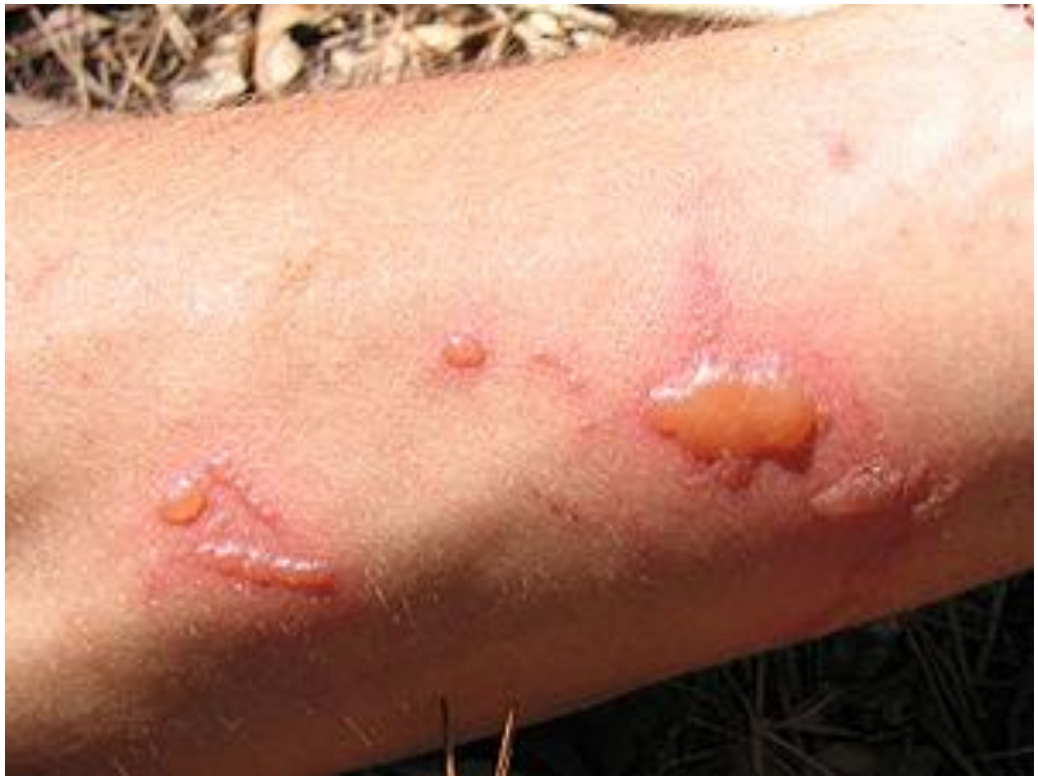
Phototoxicity

Phototoxicity (also called photoirritation) is a chemically induced skin irritation, requiring light, that does not involve the immune response

Phototoxicity is a type of photosensitivity



Three main types of phototoxic reactions

Photodegradation with formation of toxic substances

$S^* \rightarrow A^\bullet + B^\bullet$

Photosensitized oxidation reactions

$^3S^* + D \rightarrow S^{\bullet -} + D^{\bullet +}$ type I mechanism

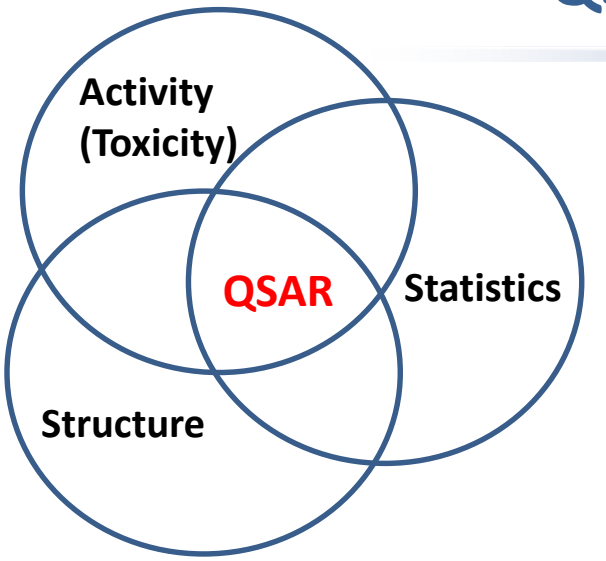
$S^{\bullet -} + O_2 \rightarrow O_2^{\bullet -}, H_2O_2$

$^3S^* + O_2 \rightarrow {}^1O_2$ type II mechanism

Formation of cyclobutane dimers and photoadducts

$S^* + dT \rightarrow dT^* \rightarrow dT{=}dT$

QSAR is a useful tool in toxicology



QSAR is also used for:

- structure-phototoxicity predictions
- photosensitizer activity predictions in PDT

In photochemistry QSPR is used for the prediction of:

- absorption wavelength
- fluorescence intensity
- photolysis rate constant/photolysis quantum yield
- rate constant of reaction with $^1O_2$

Is it possible to use QSPR to study phototoxic reactions?

Phototoxic reactions

Photodegradation with formation of toxic substances

$S^* \rightarrow A^\bullet + B^\bullet$

Well studied by QSPR

Zhang, "Predictive models on photolysis and photoinduced toxicity of organic chemicals", *2013*

Photosensitized oxidation reactions

$^3S^* + D \rightarrow S^{\bullet -} + D^{\bullet +}$

$S^{\bullet -} + O_2 + O_2 \rightarrow O_2^{\bullet -}, H_2O_2$

$^3S^* + O_2 \rightarrow {}^1O_2$

Depends on triplet formation (Φ_T)

Have not been studied by QSPR yet

Formation of cyclobutane dimers and photoadducts

$^3S^* + dT \rightarrow dT^* \rightarrow dT{=}dT$

Depends on triplet formation (Φ_T)

Have not been studied by QSPR yet

Large part of phototoxic reactions depends on triplet state formation and has not been studied yet by QSPR!

Aim - objectives

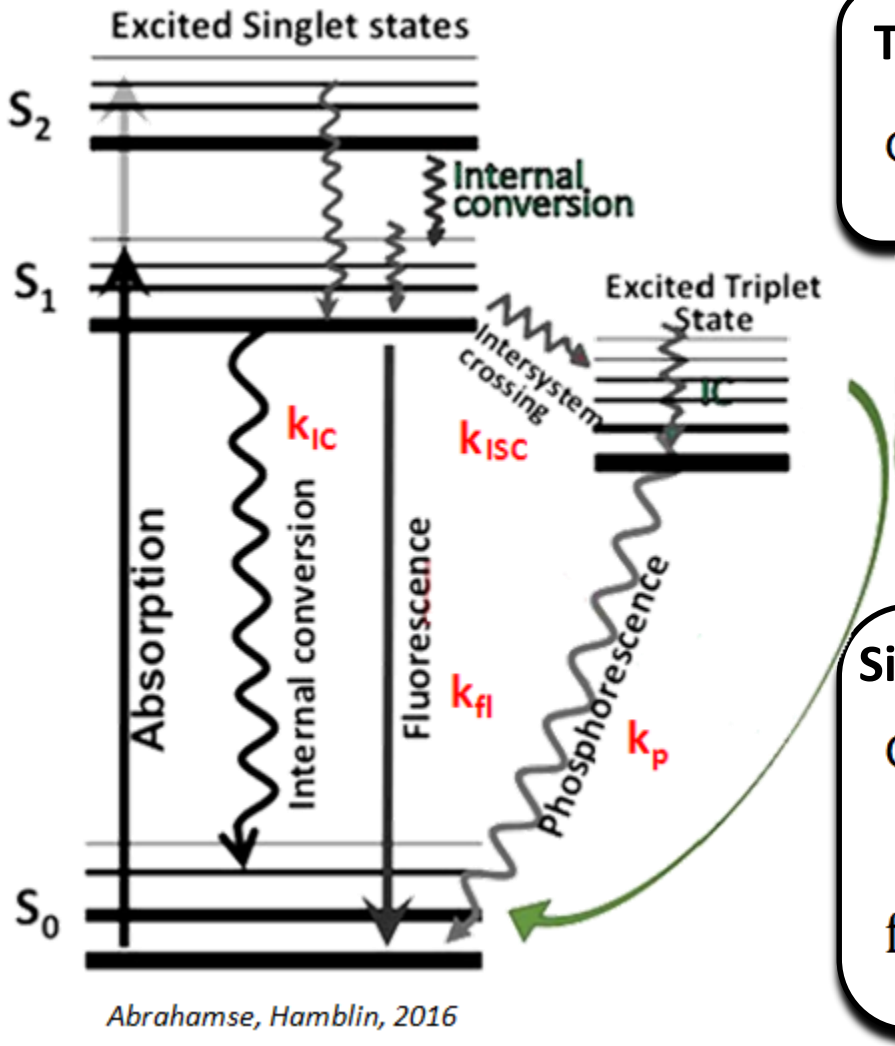
Aim

To apply QSPR methodology to the analysis of photosensitization reactions

Objectives

- To perform QSPR analysis of structure – Φ_T and structure – Φ_Δ relationships
- To build models with sufficient predictive ability
- To find new data about photosensitizers activity

Theoretical basis



Abrahamse, Hamblin, 2016

Triplet state generation quantum yield:

$$\Phi_T = \frac{k_{ISC}}{k_{ISC} + k_q + k_{fl} + k_{ic}}$$

Singlet oxygen generation quantum yield:

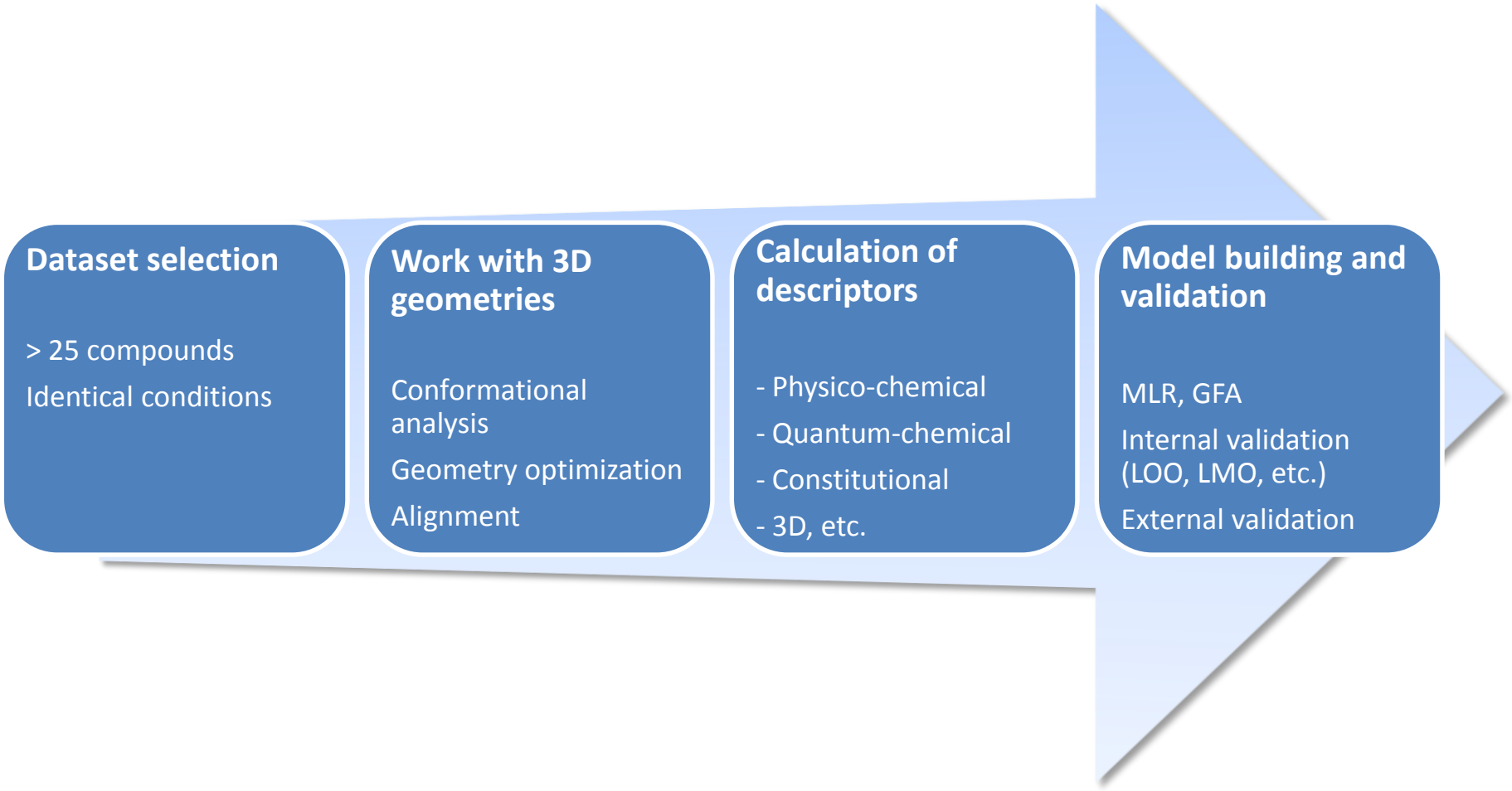
$$\Phi_\Delta = \Phi_T \, p_T^{O2} f_T^\Delta$$

$p_T^{O2} \approx 1$

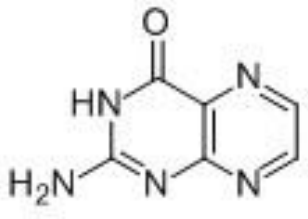
$$f_T^\Delta = \frac{k_{et}[O_2]}{k_{et}[O_2] + k_q^T[O_2] + k_p}$$

We have a rationale for applying QSPR!

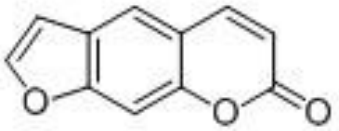
Modeling workflow



Several case studies – several classes of compounds

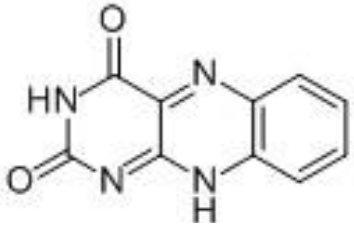


pterin

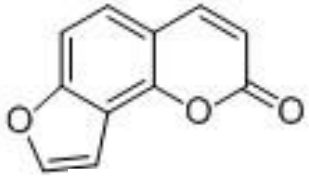


psoralen

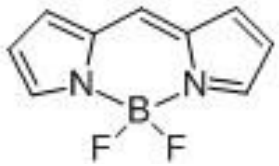
porphyrin



flavin



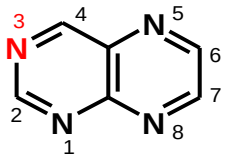
angelicin



BODIPY

QSPR study of $^1O_2$ generation by pteridines

$\Phi_\Delta = f_{MLR}(\chi, q(N^3), \mu)$



χ – electronegativity

μ – dipole moment

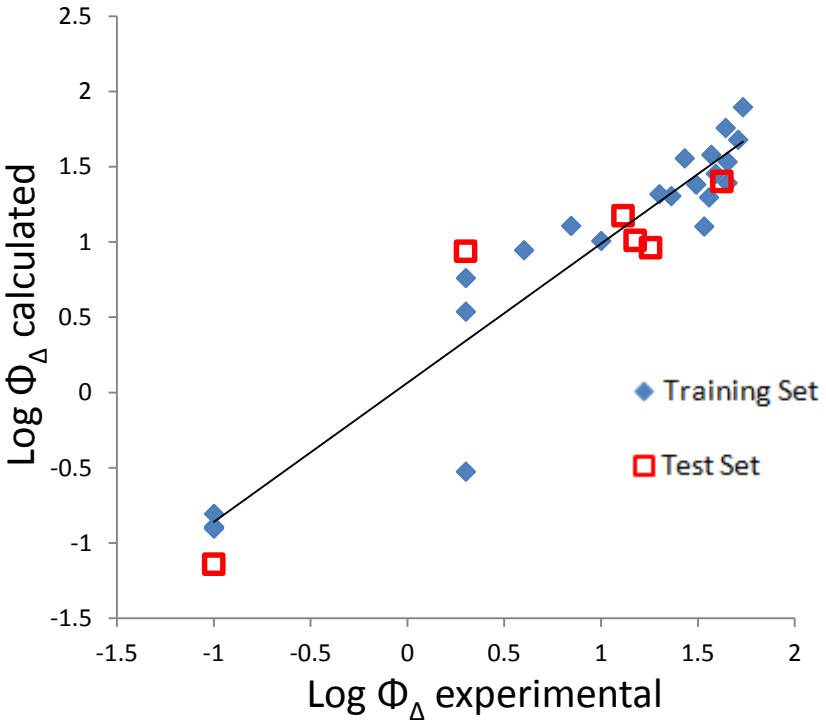
$q(N^3)$ – electrostatic atomic charge at N^3

Statistical parameters of the model

n=29; R^2 = 0.92 (sufficient if > 0.6)

q^2 = 0.88 (sufficient if > 0.6)

pred_R^2 = 0.87 (sufficient if > 0.5)



Interpretation

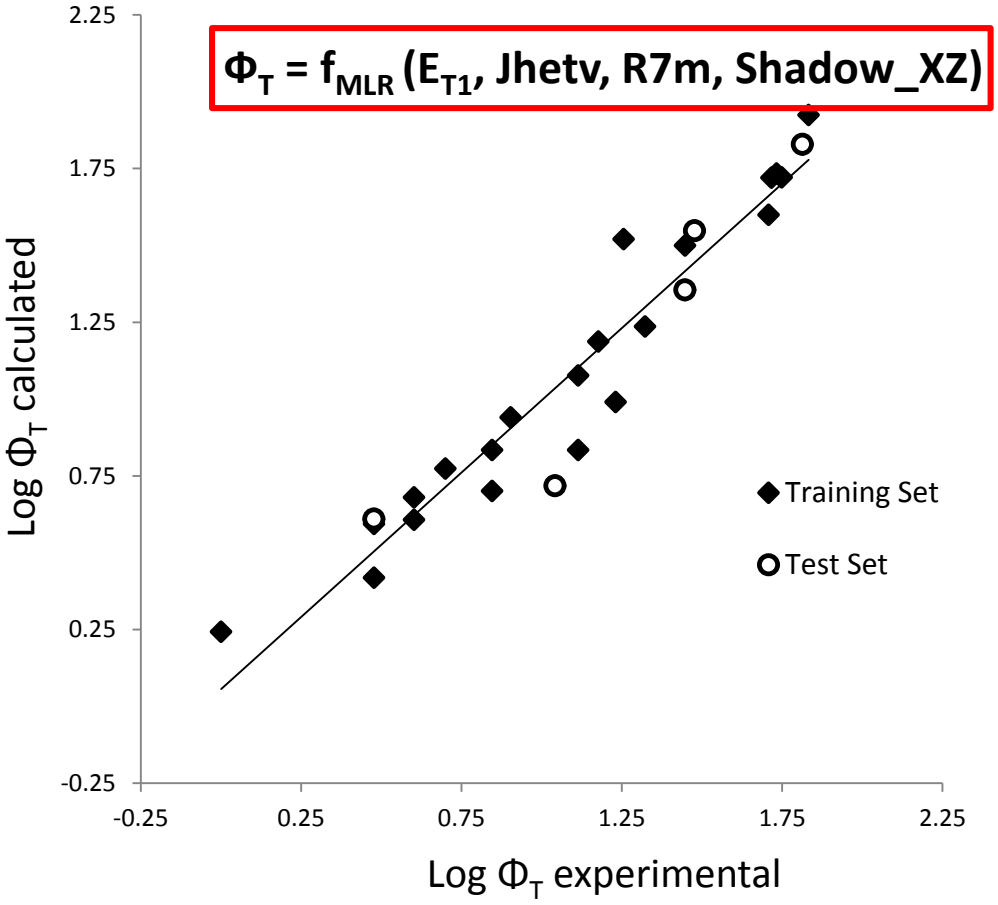
- The model possesses high internal stability and high predictive ability
- Electronegative substituents are favorable for high Φ_Δ

Buglak et al, Photochem. Photobiol. Sci., 2016

Our model effectively predicts Φ_Δ

QSPR study of T_1 generation by furocoumarins

Generation of triplets and $^1O_2$ by psoralens is a complicated matter due to the proximity of np* and pp* states



Statistical parameters of the model

n = 26

R^2 = 0.93 (sufficient if > 0.6)

q^2 = 0.86 (sufficient if > 0.6)

pred_R^2 = 0.90 (sufficient if > 0.5)

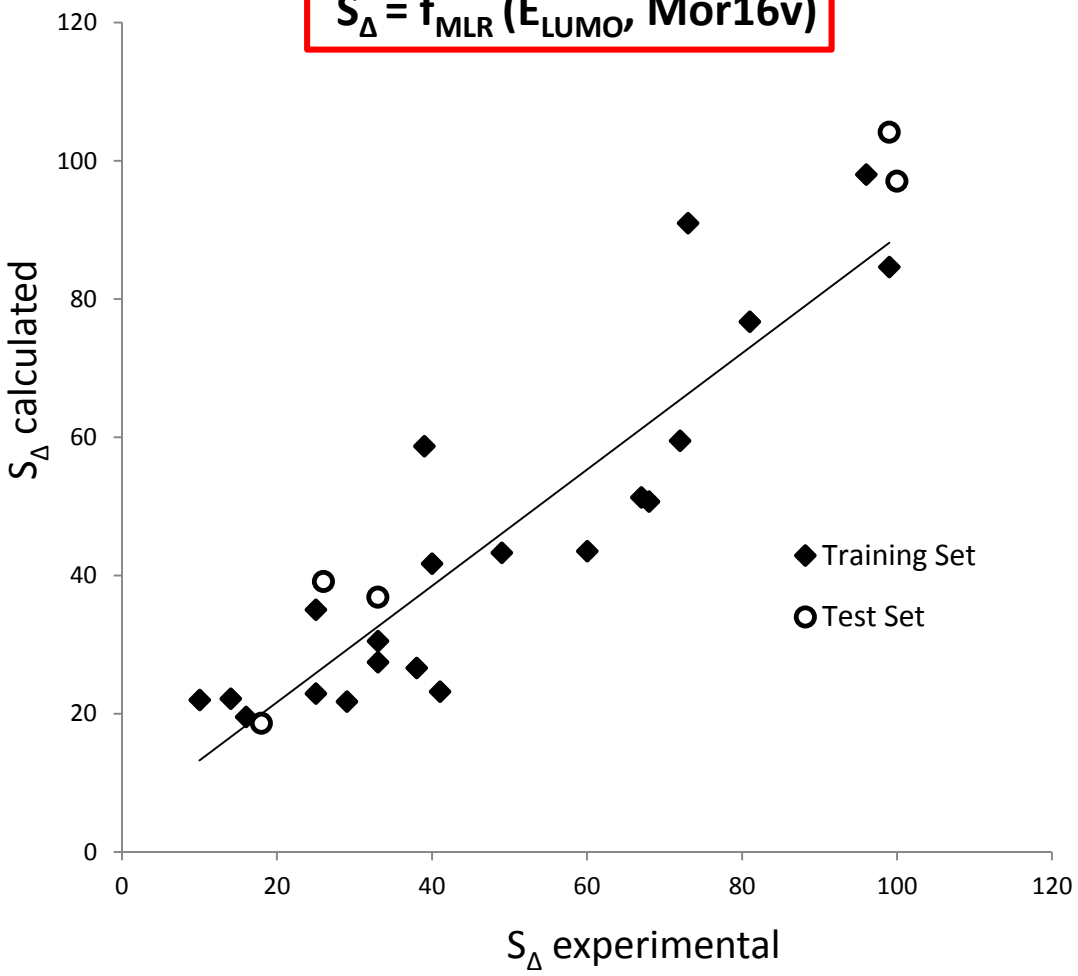
- The model possesses high internal stability and high predictive ability
- Φ_T correlates with E_{T1}
- Proximity of np* and pp* is evaluated by topological descriptors

Buglak, Kononov, New J Chem, 2018

The model effectively predicts Φ_T

QSPR study of $^1O_2$ generation by furocoumarins

$S_\Delta = f_{MLR}(E_{LUMO}, Mor16v)$



Statistical parameters of the model

n = 26

R^2 = 0.86 (sufficient if > 0.6)

q^2 = 0.81 (sufficient if > 0.6)

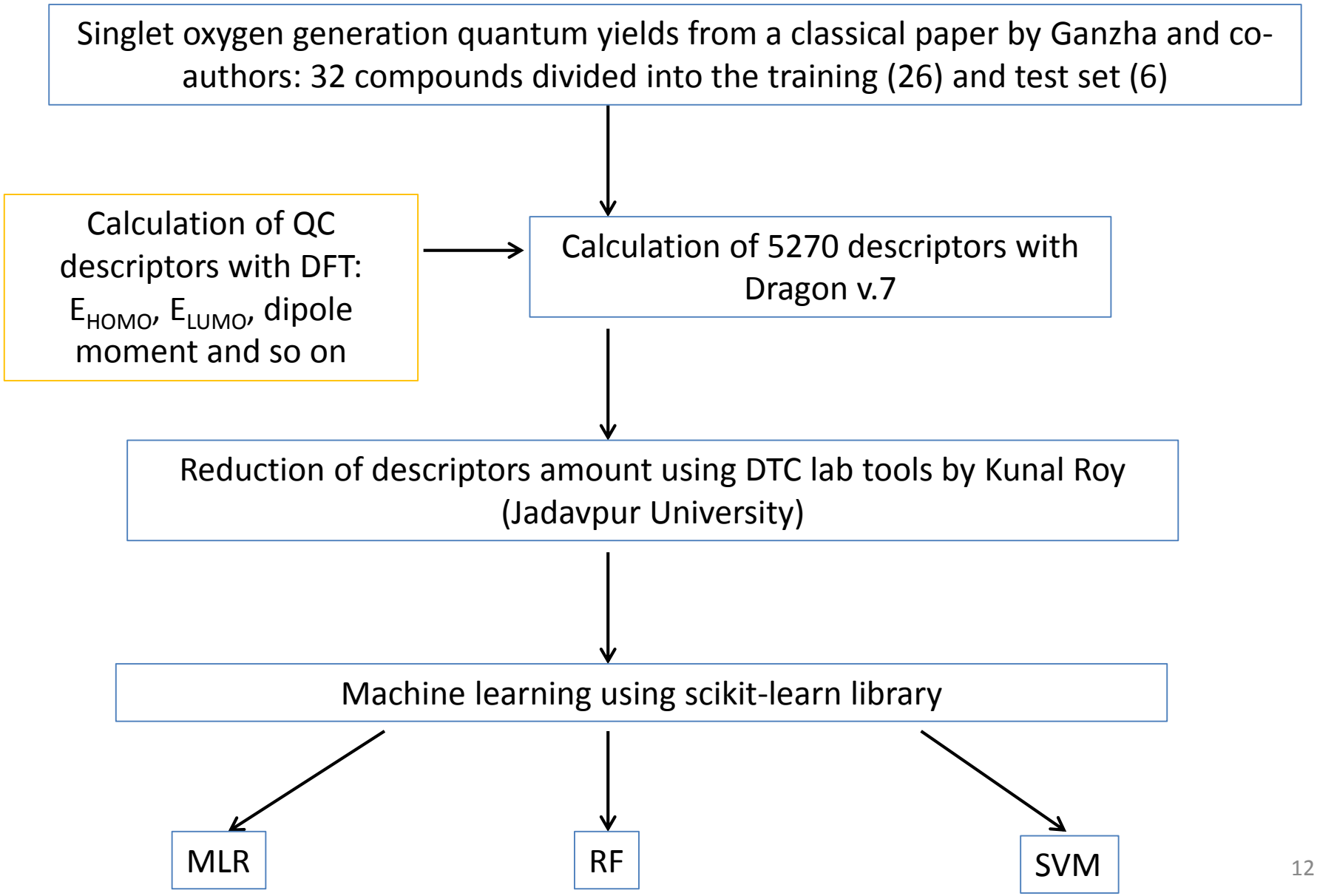
pred_R^2 = 0.97 (sufficient if > 0.5)

$S_\Delta = f_T^\Delta \times p_T^{O2}$

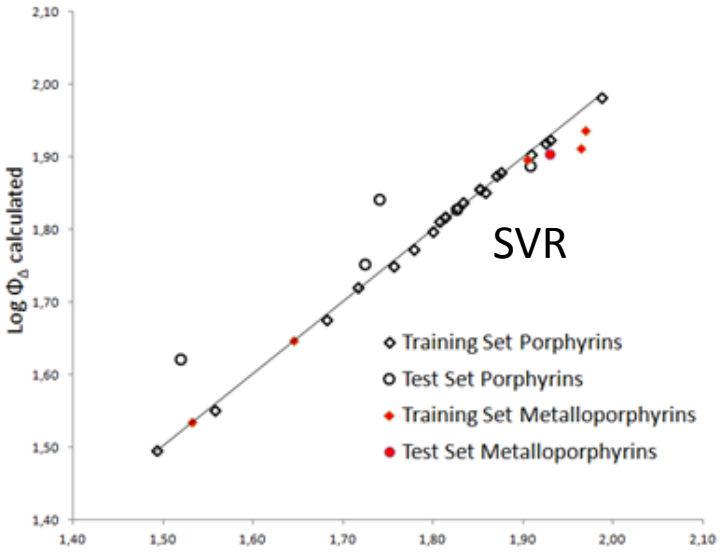
Apparently, molecules with higher electron affinity have higher S_Δ and f_T^Δ

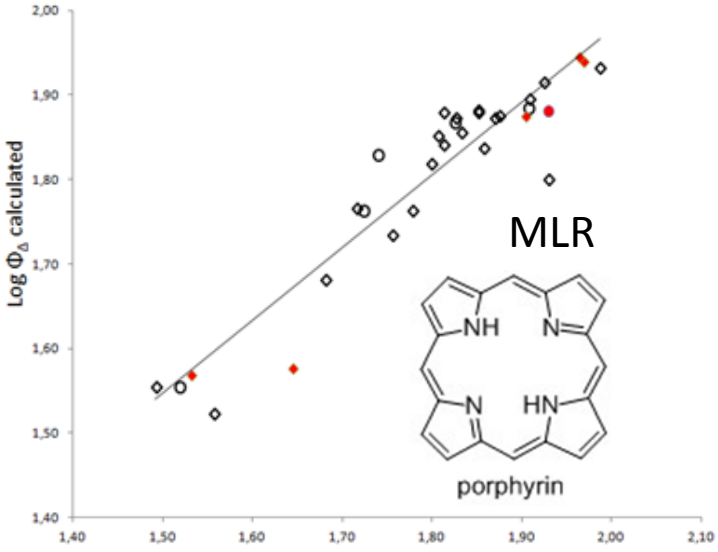
Our model effectively predicts S_Δ

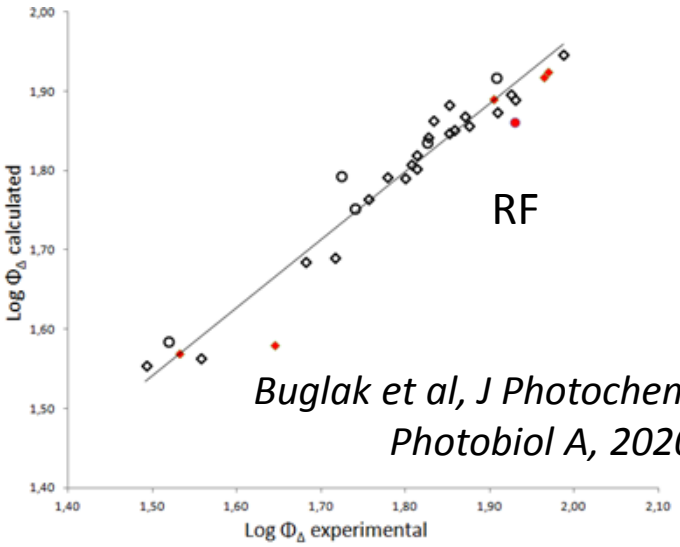
QSPR study of $^1O_2$ generation by porphyrins, the plan



QSPR study of $^1O_2$ generation by porphyrins and Zn-porphyrins







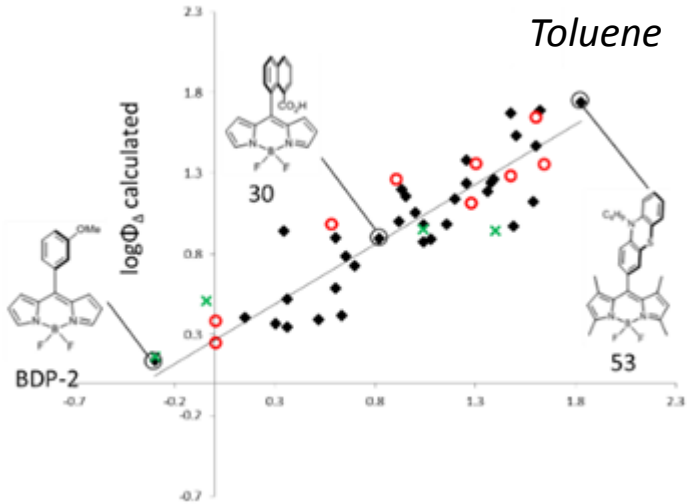
Buglak et al, J Photochem Photobiol A, 2020

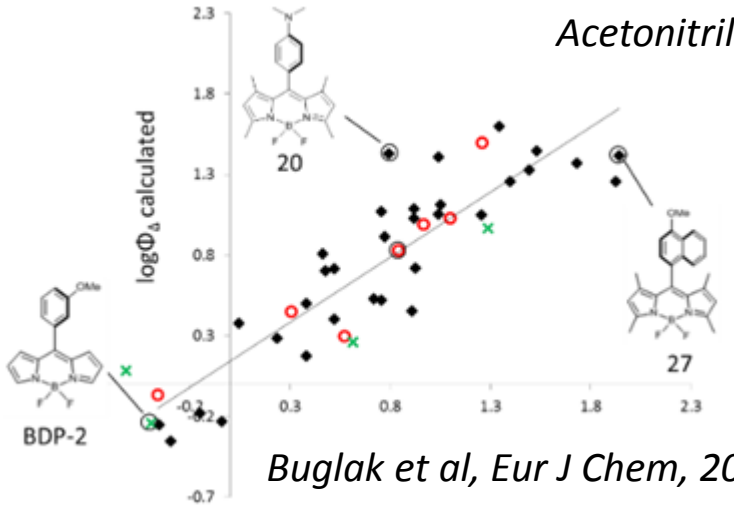
The models were built using a combination of autocorrelation, GETAWAY, topological, and quantum-chemical descriptors

Parameter	SVR	MLR	RFR
R	0.995	0.943	0.974
R^2	0.991	0.889	0.949
q^2	0.842	0.744	0.619
pred_R^2	**0.801**	**0.866**	**0.875**
RMSE	0.029	0.045	0.034
max Φ_Δ error	14.5%	21.9%	9.2%
RMS Φ_Δ error	3.5%	7.0%	4.1%

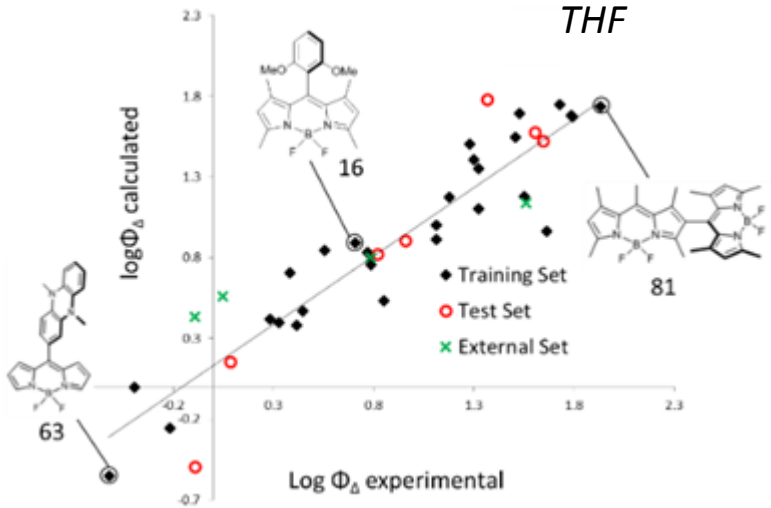
RFR model is the best one

QSPR study of $^1O_2$ generation by >70 BODIPYs





Buglak et al, Eur J Chem, 2021



Parameter	Toluene	Acetonitrile	THF
R	0.882	0.890	0.906
R^2	0.778	0.792	0.820
$R^2_{adjusted}$	0.739	0.744	0.773
RMSE	0.240	0.283	0.285
q^2	0.686	0.693	0.620
SDEP	0.306	0.344	0.414
R^2_{test}	**0.800**	**0.823**	**0.879**
$R^2_{external}$	0.635	0.722	0.584
RMS Φ_Δ error	8.2	18.3	12.0

QSPR is useful for predicting ΦΔ in media with different polarity!

Conclusions

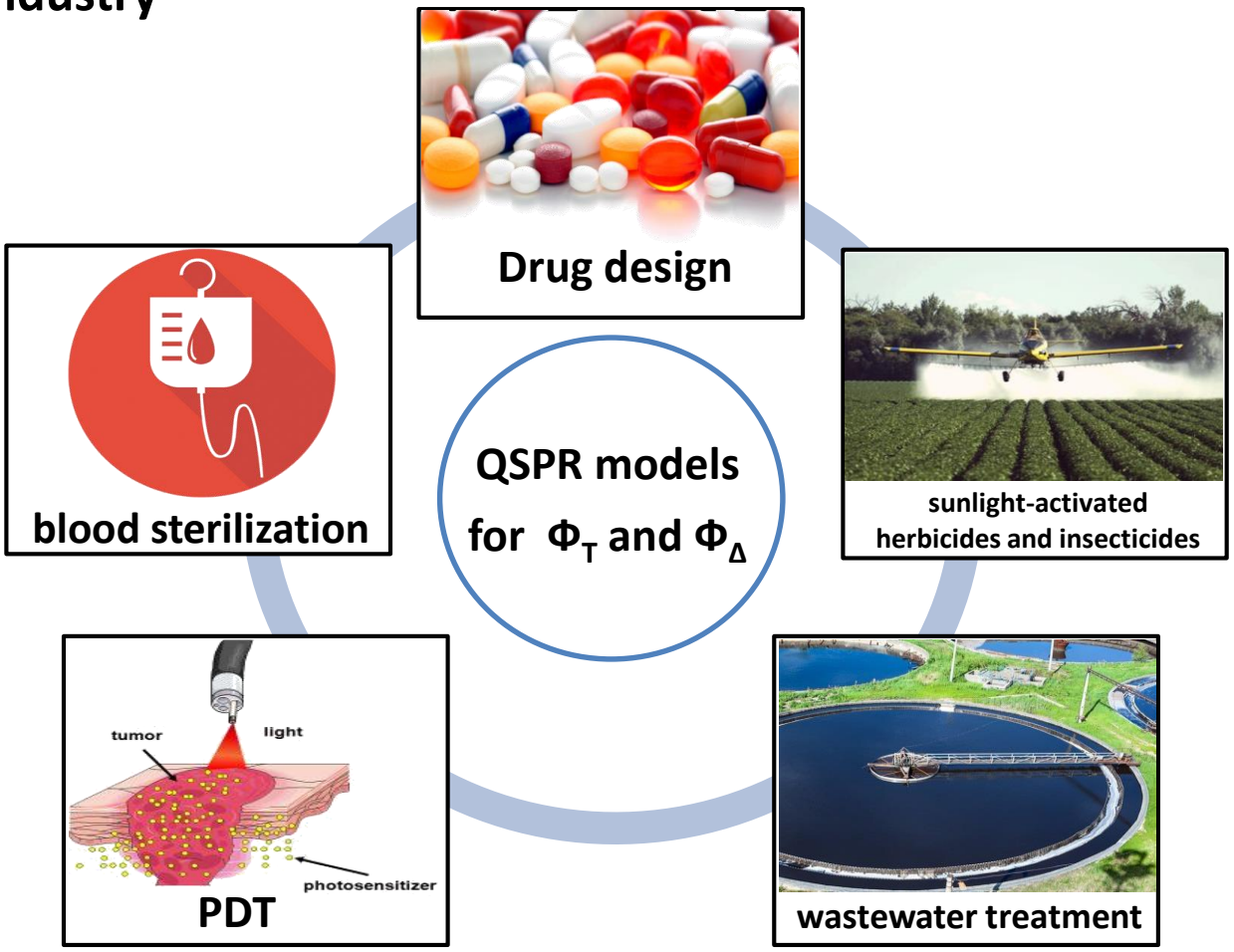
1. The QSPR models for Φ_{Δ}, Φ_{T} and S_{Δ} possess high internal stability and high predictive ability

2. For the first time correlations between structure and activity have been shown for pteridines, psoralens, and BODIPYs

3. QSPR is applicable to the study of T_1 formation and $^1O_2$ generation by organic sensitizers

Perspectives

Models "structure - triplet quantum yield" and "structure – $^1O_2$ generation quantum yield" may be beneficial not only in drug design, but also in other areas of chemical industry



Future plans

- To use QSPR in the study of triplet state lifetime, triplet state energy, etc.

- To try different classes of compounds: fluoroquinolones, anthracenes, etc.

- To find whether QSPR is applicable to the study of triplet state formation by metal-organic compounds: metalloporphyrins, ligand-protected metal nanoclusters, heavy-atom-containing BODIPYs