# Artificial Intelligence-Based Molecular Property Prediction of Photosensitizing Effects of Drugs

Amun G. Hofmann[1], Asan Agibetov[1]

1: FIFOS – Forum for Integrative Research & Systems Biology, Vienna, Austria

Corresponding Author:

Amun Hofmann

Email: ah.reply@outlook.com

## Abstract

Introduction: Drug-induced photosensitivity is an adverse event of various agents that are used in all major specialties of clinical medicine. Apart from the acute condition, an association of photosensitive events and an increased risk of skin cancer have been repeatedly reported. However, photosensitizing properties of drugs and chemical compounds are also deliberately utilized as a treatment modality, for example as photodynamic therapy in oncology. While certain chemical features have been shown to induce photosensitivity more frequently, the matter is still not conclusively understood and commonly used photobiological assays are discussed to be affected by several limitations. In the present work we investigated the feasibility of predicting photosensitizing effects of drugs and chemical compounds via state-of-the-art artificial intelligence-based workflows.

Methods: A dataset of 2,200 drugs was used to train three distinct models (logistic regression, XGBoost, and a deep learning model) to predict photosensitizing attributes based on the SMILES string. Labels were obtained from a list of previously published photosensitizers resulting in 205 photosensitizing drugs. Data was partitioned using an 80/10/10 training-validation-test split by molecular scaffold. External evaluation of the different models was performed using the tox21 dataset and included a technical interpretation of prediction scores as well as a pharmacological interpretation.

Results: ROC-AUC ranged between 0.8939 (deep learning model) and 0.9525 (XGBoost) during training, while in the test partition it ranged between 0.7785 (deep learning) and 0.7927 (XGBoost). The models were employed to facilitate predictions on the external validation set. Analysis of the top 200 compounds of each model resulted in 55 overlapping molecules. Fifteen of those were fluoroquinolones, a class of commonly reported photosensitizers. Prediction scores in this subset corresponded well with culprit substructures suspected of mediating photosensitizing effects.

Discussion: All three models appeared capable of predicting photosensitizing effects of chemical compounds. However, compared to the simpler model (logistic regression) the complex models (XGBoost and Chemprop) appeared to be more confident in their predictions as exhibited by their distribution of prediction scores. The evaluation of the models on external data further solidified the feasibility of molecular property prediction for photosensitizing abilities. A qualitative analysis of fluoroquinolones in the external dataset based on available photobiological evidence showed that their prediction scores corresponded well with their chemical structure.

## Introduction

Drug-induced photosensitivity generally refers to a cutaneous adverse reaction to systemically or topically administered pharmaceuticals.[1] Photosensitivity reactions are generally classified as phototoxic and photoallergic, with photo-onycholysis either being described as a special case of phototoxicity or a distinct adverse effect.[2] All photosensitizing molecules act as chromophores when receiving electromagnetic radiation of a distinct wave length. However, the subsequent molecular pathways and eventual cellular targets differ among the drugs.[3] Photosensitive lesions can only develop in skin areas receiving light and primarily depend on ultraviolet (UV) A exposure as opposed to regular sunburns that are UVB mediated.[2] Phototoxic effects due to systemically administered agents are the most prevalent form of drug-induced photosensitivity.[4] The leading symptom is erythema but patients can also present with burning or prickling skin sensations and even pseudoporphyria.[5]

However, photosensitizing properties of specific agents are also used therapeutically in photodynamic therapy. Clinical applications can be found in ophthalmology for age-related macular degeneration[6], in oncology for several types of cancer[7,8] and in dermatology for various indications[9–11]. Extracorporeal photopheresis with psoralen and UVA (PUVA) is another distinct treatment modality that is based on the photosensitizing ability of psoralen.[12]

Photosensitizing effects as an adverse drug reaction are of great clinical interest. This is based not only on the acute phototoxic or photoallergic reactions but also on a potentially increased risk of subsequent skin cancer since photocarcinogenic effects have been shown for several photosensitizing drugs.[13] Regulatory bodies such as the Food and Drug Administration (FDA) or European Medicines Agency (EMA) therefore require photobiological testing upon the approval of new drugs. The most common assay used is the in-vitro-3T3-NRU test. However, while being accepted as reasonably sensitive its specificity is debated.[14]

The inter-disciplinary convergence of chemistry and machine as well as deep learning is a growing area of research. Cheminformatics aid the comprehension of existing complex

chemical data and allow designing as well as conducting experiments *in silico*. The computational prediction of molecular properties has gained a lot of interest in both biomedical research as well as in the industrial sector. Instead of screening hundreds or thousands of molecules and compounds via traditional wet-lab assays, deep chemistry enables rapid exploration of potential agents with distinct molecular properties.[15]

In the present project we investigated the ability of different machine and deep learning algorithms to predict photosensitizing effects of drugs and chemical compounds.

## Methods

### Data

The initial training dataset consists of 2,220 drugs from the Human Metabolome Database (Supplement File 1). The drugs were classified based on their photosensitizing abilities (1 = photosensitizing, 0 = non-photosensitizing) via string matching of the drug name with a dataset from a previous project on drug-induced photosensitivity.[2] In brief, MEDLINE and professional drug reaction databases were screened for agents that are reported to cause phototoxic or photoallergic adverse events. In summary, drugs that were found to have a peer-reviewed scientific publication addressing their photosensitizing effects were compiled and classified as photosensitizing. The full dataset included 205 (9.2%) photosensitizing drugs. The data was partitioned using an 80/10/10 training-validation-test split by molecular scaffold. Hyperparameter optimization has been performed on the validation set while the final reported prediction metrics are based on the test set (holdout set). Therefore, no double-dipping into the training dataset has been performed. External evaluation was performed using the tox21 dataset after removal duplicates already found in the training data. Tox21 dataset is a result of the Toxicology in the 21$^{st}$ Century project that contains property information on >8,000 chemical.[16]

### Deep learning model

For the present project we used the open-source library Chemprop.[17] Chemprop uses a message passing neural network to learn to predict molecular properties from the graph structure of a given molecule. The graphs are constructed based on the SMILES string of the respective molecule. Hyperparameter optimization was performed based on a Bayesian approach (tree-structured parzen estimator) with 50 iterations. The final set of hyperparameters used for training is shown in Supplement File 2. The eventual training was performed with 10-fold cross-validation with ensembles (30 models in total). Furthermore, Chemprop enables the addition of molecule-, bond- or atom-level features via RDKit. We used pre-normalized RDKit molecule-level features to further improve model performance. An

average of the 30 models was then used to for prediction, where each molecule receives a score between 0 and 1 reflecting its ability to cause photosensitive eruptions (0 = none).

## Machine learning models

Molecules represented by SMILES strings in the original dataset were converted to circular fingerprints of 1024 bits. To compare the performance of algorithms of different complexity, we decided to train models both via logistic regression and XGBoost. They were applied to the circular fingerprints with hyperparameter optimization for 100 iterations and 5-fold cross-validation. Hyperparameter tuning included L1, L2, and elastic net regularization for 100, 200, 500, or 1000 iterations applying a random penalty strength between 1e-6 and 100 for logistic regression. For XGBoost, 20, 50, 100, 200, or 400 boosting trees were built applying different learning rates, child weights, loss reduction cut-offs, and regularization parameters (L1 and L2). The models were evaluated based on ROC-AUC.

## External evaluation

To simulate a rea-world scenario where a trained model in a controlled environment is applied on related but external data, we proposed to perform a two-step external evaluation. In the first step we aimed at testing the generalization capacity of the model by comparing prediction score distributions on both the controlled environment and external data (tox21). In particular, we wanted to investigate whether the model was guessing that an unseen compound possesses photosensitizing abilities or if it was making an informed decision. In the second step a pharmacological interpretation was performed relying on published, peer-reviewed scientific literature.

# Results

## Prediction of photosensitizing ability

In total, 1,998 unique SMILES were part of the training and validation set, while 222 formed the test set. The external evaluation set (tox21) contains 7,831 molecules. However, 771 and 98 were found to be duplicates of molecules in the training and test partition, respectively, and were therefore excluded for external evaluation. ROC-AUC scores on the training partition were high (0.89 – 0.94) for the best performing fold for all three models with XGBoost showing the highest performance. ROC-AUC scores were lower in the test partition but acceptable in all cases (0.78 – 0.79). (see Table 1) Qualitative analysis of prediction scores was performed to estimate prediction thresholds in the external evaluation set and account for the imbalanced frequency of photosensitizing drugs in the training data. Chemprop and XGBoost showed skewed distributions around the incidence rate of photosensitizing molecules in both partitions. Logistic regression, in contrast, resulted in normally distributed predictions. (see Figure 1)

## Generalization of prediction of photosensitizing ability on external data

### *Prediction score consistency in controlled and external datasets*

The external evaluation was conducted via a two-step approach, a technical analysis and a pharmacological interpretation. For all models the predictions on the external evaluation set replicated the distribution of the training and test partitions, thereby exhibiting consistency. (see Figure 1) The highest prediction scores regarding both maximum and mean were obtained by logistic regression. However, evaluation metrics could not be calculated since the external evaluation set contained no ground truth labels, i.e. the only molecules in the tox21 dataset with known photosensitizing abilities prior to the conducted analyses were excluded as duplicates of the training data.

### *Pharmacological interpretation*

To further explore agents in the external evaluation set, we selected overlapping compounds from the top 200 predictions of each model. This resulted in 55 agents. The predictions of

those ranged from 0.658 to 0.864 for the logistic regression-based model, from 0.211 to 0.771 for the XGBoost model, and from 0.336 to 0.682 for Chemprop. Fifteen (27.3%) were fluoroquinolones and 6 (10.9%) were thiazides, two drug classes commonly reported as examples of drugs inducing photosensitive reactions. Other drug classes featuring reported photosensitizers included 2 tetracyclines, 2 coxibs, 2 sulfonamides (all 3.6%), 1 sulfonylurea, and 1 2-arylpropionic acid derivative (profen) (both 1.8%). Additionally, one of the drugs (furosemide) was part of the original compilation of photosensitizing drugs but not included in the training data due to the assembling strategy (see Methods). Literature research regarding published evidence on photosensitizing effects of the remaining 25 agents was conducted. However, since the external evaluation data mostly consisted of molecules not used in clinical medicine most queries had no results. Nevertheless, for rufinamide and meticrane reports on potential photosensitizing effects were discovered while fomesafen is a light-dependent peroxidizing herbicide relying on photoactivation.

*Fluoroquinolones*

Since the cumulative body of evidence regarding photosensitive effects induced by fluoroquinolones is among the most profoundly investigated in the field, we conducted a sensitivity analysis on this subgroup of overlapping compounds. It has been previously shown that the photosensitizing ability of fluoroquinolones is largely mediated by the structural components at the R1[18] and R8[19,20] position. A schematic depiction of the fluoroquinolone core structure and the R1 and R8 positions is given in Figure 2. Using the mean of all three models it was observed that the algorithms associate aryl halides incorporating 2 fluor atoms at the R1 position with a higher probability of causing photosensitive eruptions, followed by mono-fluorinated aryl halides at R1, and single fluor atoms at R1 or R8. Absence of fluor often accompanied by a bond between the R1 and R8 position resulted in lower average predictions. (see Table 2) Additionally, we conducted an automated interpretation of the molecules to identify the substructures driving prediction scores of the deep learning model using a Monte Carlo Tree Search incorporated in Chemprop. The results are shown in Supplementary Figure

S1. In all cases either the bicyclic core structure or one of the two cyclic components serving as the foundation of fluoroquinolones were identified as the responsible substructure. This further validates the feasibility of deep learning models to identify chemical compounds capable of inducing photosensitive reactions.

## Discussion

Based on the obtained prediction metrics both machine and deep learning models appear to facilitate molecular property prediction regarding photosensitizing effects. While testing simple (logistic regression) and complex (XGBoost) machine learning algorithms as well as a deep learning model (Chemprop) the performances were comparable. XGBoost showed the highest ROC-AUC both during training and in the test partition. The distribution of prediction scores was skewed with Chemprop and XGBoost, which indicates that they might pattern match photosensitizing properties more accurately. With logistic regression the distributions were normal suggesting that overall, the model is not confident in its predictions, and therefore the cut-off between photosensitizing and non-photosensitizing features may not be clear for the model. However, XGBoost also had the biggest difference in performance between training and test sets. Since the generalization gap can be interpreted as a surrogate for overfitting during training this might indicate that more complex algorithms are prone to overfitting in the case of limited datasets as in our study.

After establishing the models, they were applied to a dataset frequently used for external evaluation (tox21). Analysis of the 200 molecules with the highest predictions for each model showed some divergence as only 55 (27.5%) overlapping chemical compounds were found. Thirty of those were drugs that belong to classes frequently reported to induce photosensitivity reactions such as fluoroquinolones or thiazide diuretics, indicating solid validity. Literature research on the remaining 25 molecules retrieved sparse results. However, since the majority of molecules in the validation set are not pharmacological agents used in human medicine, this is not surprising, and for two drugs (rufinamide and meticrane) not included in the original dataset that provided classification labels, published evidence was found indicating photosensitizing abilities. A detailed subgroup analysis of fluoroquinolones in this set showed the mean prediction corresponded well with structural components of the molecules that have been reported to induce photosensitizing effects, primarily the halogens at the R1 and R8 positions. Additionally, an atomic bond between those positions was correlated with lower

predictions. This could be a reflection of limited photosensitizing abilities in the absence of fluor atoms at the R1 and R8 positions, but it could also indicate that such a structure alters molecular properties. This could induce further photochemical/-biological exploration.

Limitations of our models are partially based on the workflow. Since labels regarding photosensitizing effects were compiled from the scientific literature and not photobiological tests is possible that the list of photosensitizing drugs includes false positives. The low quality of evidence in this regard has been previously discussed.[21] Additionally, fluoroquinolones constituted approximately 8% of the training. This could result in overweighting their structural components and thereby increase their prediction scores – the models might be biased towards them. However, while this might limit the interpretation of prediction scores of fluoroquinolones in relation to other compounds, the intra-group comparative analysis corresponded very well with photobiological data showing that within fluoroquinolones lower predictions might capture a lower risk for photosensitizing effects accordingly. While establishing models based on quantitative data from photobiological/-dermatological tests might improve the accuracy of predictions, our work shows that predicting photosensitizing effects of drugs and chemical compounds based on scientific literature is feasible.

Considering the ongoing quest to optimize photosensitizers for photodynamic therapy from a pharmaceutical point of view to maximize treatment benefits while mitigating adverse effects[22], the introduction of A.I. assisted molecular property prediction might hold great potential to aid these efforts.

## Figures and Tables

**Figure 1.** Histograms of prediction scores for each model in the training/validation set (A), the test set (B), and the external evaluation set (C).

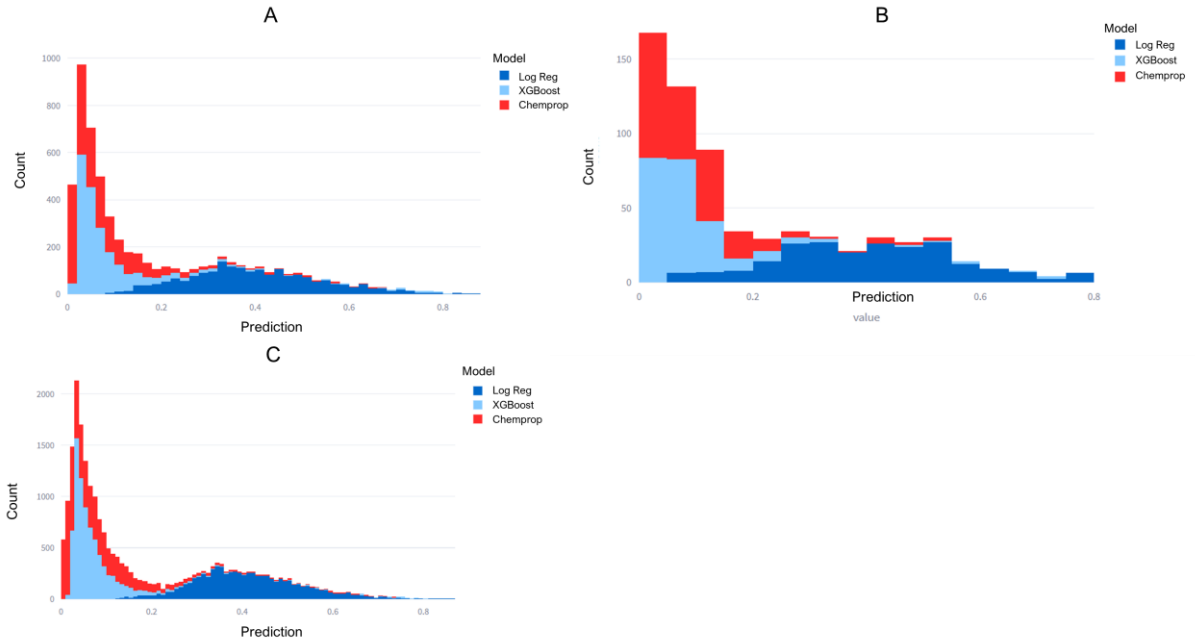



**Figure 2.** Fluoroquinolone core structure with its R1 and R8 positions (based on ciprofloxacin).

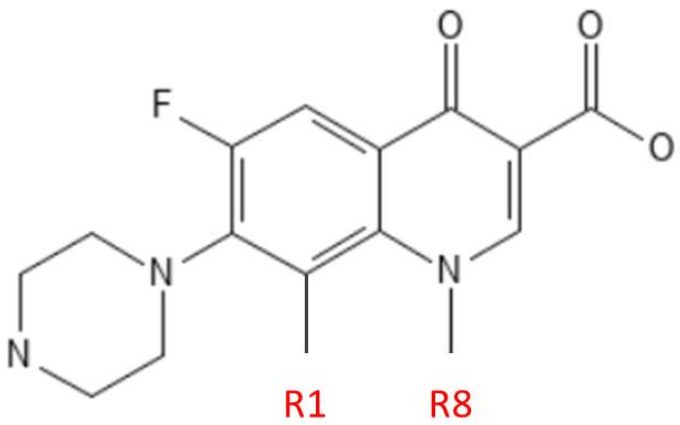


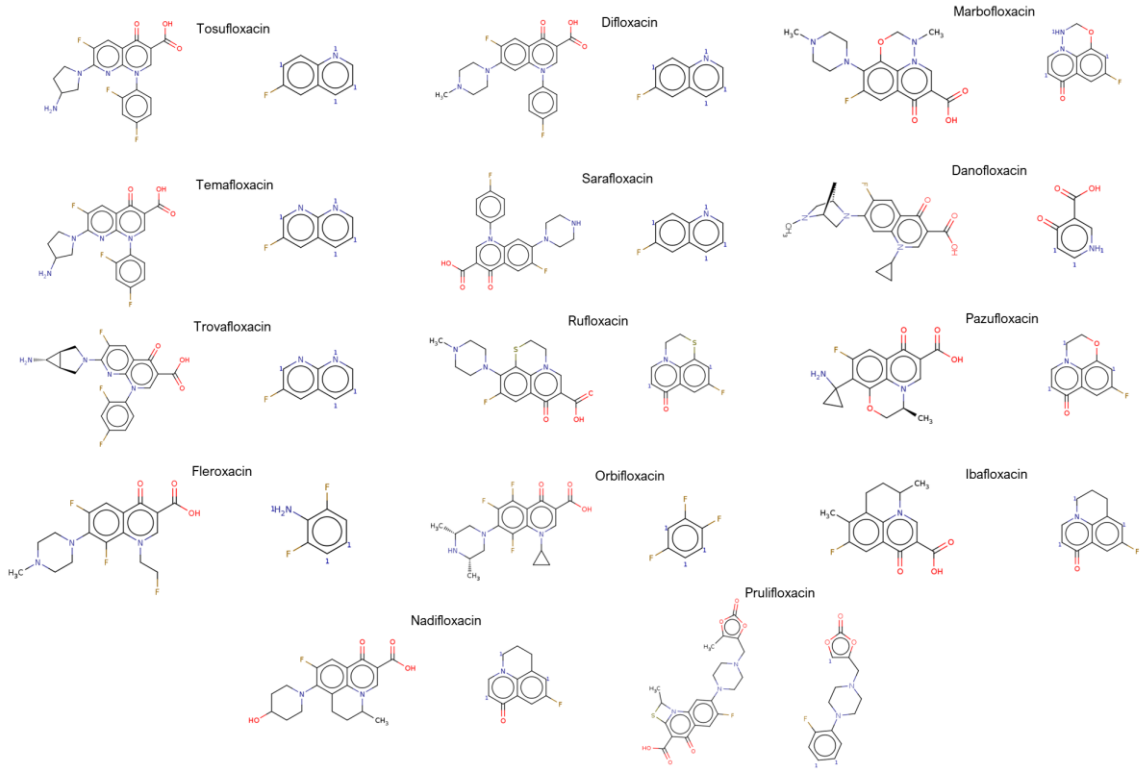
**Table 1.** ROC-AUC of different algorithms on the original dataset stratified by partition.

| Dataset | Model | ROC-AUC |
|---|---|---|
| **Training** | XGBoost | 0.9425 |
| **Training** | Logistic Regression | 0.9088 |
| **Training** | Chemprop | 0.8939 |
| **Test** | XGBoost | 0.7927 |
| **Test** | Logistic Regression | 0.7859 |
| **Test** | Chemprop | 0.7785 |

**Table 2.** Fluroquinolones within the set of overlapping drugs with the highest predictions ranked by mean score of the three models. The table depicts both the prediction scores of the three models as well as information on their substructure at the first (R1) and eighth (R8) position and whether there is a bond between them (R1-R8).

| Name | Formula | Log Reg | XGBoost | Chemprop | R1 | R8 | R1-R8 |
|---|---|---|---|---|---|---|---|
| **tosufloxacin** | C19H15F3N4O3 | 0.864 | 0.771 | 0.656 | Aryl halide (2F) | - | |
| **temafloxacin** | C21H18F3N3O3 | 0.836 | 0.760 | 0.682 | Aryl halide (2F) | - | |
| **trovafloxacin** | C20H15F3N4O3 | 0.843 | 0.752 | 0.647 | Aryl halide (2F) | - | |
| **fleroxacin** | C17H18F3N3O3 | 0.790 | 0.757 | 0.597 | F | F | |
| **difloxacin** | C21H19F2N3O3 | 0.823 | 0.707 | 0.607 | Aryl halide (F) | - | |
| **sarafloxacin** | C20H17F2N3O3 | 0.768 | 0.667 | 0.612 | Aryl halide (F) | - | |
| **rufloxacin** | C17H18FN3O3S | 0.776 | 0.746 | 0.502 | S | - | X |
| **orbifloxacin** | C19H20F3N3O3 | 0.743 | 0.597 | 0.671 | - | F | |
| **marbofloxacin** | C17H19FN4O4 | 0.746 | 0.733 | 0.459 | N | O | X |
| **danofloxacin** | C19H20FN3O3 | 0.774 | 0.665 | 0.444 | - | - | |
| **pazufloxacin** | C16H15FN2O4 | 0.774 | 0.660 | 0.412 | - | O | X |
| **ibafloxacin** | C15H14FNO3 | 0.741 | 0.562 | 0.453 | - | - | X |
| **nadifloxacin** | C19H21FN2O4 | 0.704 | 0.612 | 0.365 | - | - | X |
| **flumequine** | C14H12FNO3 | 0.689 | 0.478 | 0.504 | N | - | X |
| **prulifloxacin** | C21H20FN3O6S | 0.705 | 0.363 | 0.500 | - | - | |

**Supplementary Figure S1.** Automated interpretation of the fluoroquinolones and the substructure associated with their photosensitizing effects.




243

## References


1. Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol*. 1995;33(4):551-573; quiz 574-576. doi:10.1016/0190-9622(95)91271-1

2. Hofmann GA, Weber B. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. *J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG*. 2021;19(1):19-29. doi:10.1111/ddg.14314

3. Klelemen H, Hancu G, Kacsó E, Papp LA. Photosensitivity Reactions Induced by Photochemical Degradation of Drugs. *Adv Pharm Bull*. 2022;12(1):77-85. doi:10.34172/apb.2022.010

4. Selvaag E. Clinical drug photosensitivity. A retrospective analysis of reports to the Norwegian Adverse Drug Reactions Committee from the years 1970-1994. *Photodermatol Photoimmunol Photomed*. 1997;13(1-2):21-23. doi:10.1111/j.1600-0781.1997.tb00103.x

5. Di Bartolomeo L, Irrera N, Campo GM, et al. Drug-Induced Photosensitivity: Clinical Types of Phototoxicity and Photoallergy and Pathogenetic Mechanisms. *Front Allergy*. 2022;3:876695. doi:10.3389/falgy.2022.876695

6. Cruess AF, Zlateva G, Pleil AM, Wirostko B. Photodynamic therapy with verteporfin in age-related macular degeneration: a systematic review of efficacy, safety, treatment modifications and pharmacoeconomic properties. *Acta Ophthalmol (Copenh)*. 2009;87(2):118-132. doi:10.1111/j.1755-3768.2008.01218.x

7. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. *CA Cancer J Clin*. 2011;61(4):250-281. doi:10.3322/caac.20114

8. Gunaydin G, Gedik ME, Ayan S. Photodynamic Therapy for the Treatment and Diagnosis of Cancer–A Review of the Current Clinical Status. *Front Chem*. 2021;9:686303. doi:10.3389/fchem.2021.686303

9. Prayogo SA, Andrew H, Cong S, Intaran KDA. Photodynamic therapy in the treatment of condyloma acuminata: A systematic review of clinical trials. *Int J STD AIDS*. Published online November 24, 2022:9564624221138351. doi:10.1177/09564624221138351

10. Li A, Fang R, Mao X, Sun Q. Photodynamic therapy in the treatment of rosacea: A systematic review. *Photodiagnosis Photodyn Ther*. 2022;38:102875. doi:10.1016/j.pdpdt.2022.102875

11. Worley B, Harikumar V, Reynolds K, et al. Treatment of actinic keratosis: a systematic review. *Arch Dermatol Res*. Published online December 1, 2022. doi:10.1007/s00403-022-02490-5

12. Cho A, Jantschitsch C, Knobler R. Extracorporeal Photopheresis-An Overview. *Front Med*. 2018;5:236. doi:10.3389/fmed.2018.00236

13. George EA, Baranwal N, Kang JH, Qureshi AA, Drucker AM, Cho E. Photosensitizing Medications and Skin Cancer: A Comprehensive Review. *Cancers*. 2021;13(10):2344. doi:10.3390/cancers13102344

14. Kowalska J, Rok J, Rzepka Z, Wrześniok D. Drug-Induced Photosensitivity-From Light and Chemistry to Biological Reactions and Clinical Symptoms. *Pharm Basel Switz*. 2021;14(8):723. doi:10.3390/ph14080723

15. Shen J, Nicolaou CA. Molecular property prediction: recent trends in the era of artificial intelligence. *Drug Discov Today Technol*. 2019;32-33:29-36. doi:10.1016/j.ddtec.2020.05.001

16. Richard AM, Huang R, Waidyanatha S, et al. The Tox21 10K Compound Library: Collaborative Chemistry Advancing Toxicology. *Chem Res Toxicol*. 2021;34(2):189-216. doi:10.1021/acs.chemrestox.0c00264

17. Stokes JM, Yang K, Swanson K, et al. A Deep Learning Approach to Antibiotic Discovery. *Cell*. 2020;180(4):688-702.e13. doi:10.1016/j.cell.2020.01.021

18. Hayashi N, Nakata Y, Yazaki A. New findings on the structure-phototoxicity relationship and photostability of fluoroquinolones with various substituents at position 1. *Antimicrob Agents Chemother*. 2004;48(3):799-803. doi:10.1128/AAC.48.3.799-803.2004

19. Yabe K, Goto K, Jindo T, Sekiguchi M, Furuhama K. Structure-phototoxicity relationship in Balb/c mice treated with fluoroquinolone derivatives, followed by ultraviolet-A irradiation. *Toxicol Lett*. 2005;157(3):203-210. doi:10.1016/j.toxlet.2005.02.006

20. Zelmat Y, Rousseau V, Chebane L, Montastruc JL, Bagheri H, Sommet A. Fluoroquinolone-Induced Photosensitivity: A Chemical Fragment-Based Approach by a Case/Non-case Study in VigiBase®. *Drug Saf*. 2020;43(6):561-566. doi:10.1007/s40264-020-00917-4

21. Kim WB, Shelley AJ, Novice K, Joo J, Lim HW, Glassman SJ. Drug-induced phototoxicity: A systematic review. *J Am Acad Dermatol*. 2018;79(6):1069-1075. doi:10.1016/j.jaad.2018.06.061

22. Mariño-Ocampo N, Dibona-Villanueva L, Escobar-Álvarez E, et al. Recent Photosensitizer Developments, Delivery Strategies and Combination-based Approaches for Photodynamic Therapy†. *Photochem Photobiol*. 2023;99(2):469-497. doi:10.1111/php.13749