AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Psoralen Analogues with Reduced Phototoxicity: Structural Strategies, Biological Mechanisms, and Computational Opportunities

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ABSTRACT

Psoralen is an endogenous compound with a linear furocoumarin structure, having a tricyclic structure in which coumarin and furan ring are present. The psoralen and its analogues are highly researched compounds in medicinal chemistry due to their various biological activities and use in photochemotherapy. It is known for its therapeutic activity in association with DNA interaction and photochemical reactions after exposure to ultraviolet A (UVA) light. Psoralen has the capability of forming a covalent adduct with the pyrimidine bases; however, further photochemical reactions may lead to formation of DNA interstrand cross-linking, affecting the replication and transcription of DNA. These reactions are responsible for the therapeutic action of psoralen but may also lead to phototoxicity and DNA damage. Modification in psoralen structure may be helpful in finding analogues with biological activity without phototoxicity. Changes in specific sites, such as C5 and C8, along with the modification of functional groups and heterocycles, have been proposed as methods for studying the properties of molecules. Molecular docking, physicochemical analysis, and ADMET prediction may help in screening potential compounds. Nevertheless, it is impossible to prove by computational models that the compounds are less phototoxic or capable of action without UVA.

Keywords: Psoralens; Furocoumarins; Phototoxicity; UVA radiation; Psoralen analogs; SAR study; Molecular docking; Computer-aided drug design; ADMET study.

*Corresponding Author Name: Alfina F
Received 12 September 2026, Accepted 06 October 2026

Please cite this article as: Alfina F *et al*., Psoralen Analogues with Reduced Phototoxicity: Structural Strategies, Biological Mechanisms, and Computational Opportunities. American Journal of PharmTech Research 2026.

INTRODUCTION

Psoralen is a naturally produced linear furocoumarin that has a fused tricyclic structure that has a coumarin and a furan rings. Psoralen and other furocoumarins have become of great interest in medicine owing to their wide range of biological activities and use in photochemotherapy. Different psoralen derivatives such as methoxsalen (8-methoxypsoralen) and 5-methoxypsoralen have been examined in relation to their use in the treatment of dermatological disorders, including psoriasis and vitiligo [1,2].

The pharmacologic activity of psoralen depends on its ability to interact with DNA molecules. After UVA exposure, psoralen forms photoadducts with pyrimidine bases, especially thymine. The formation of further photochemical products leads to the formation of inter-strand crosslinks that affect DNA replication and transcription. These effects are used in phototherapeutic action of psoralen but may also cause cell toxicity [2,3].

Phototoxicity is a major drawback of psoralen derivatives. In the presence of photosensitizing agents furocoumarins, UVA irradiation could lead to skin irritation and erythema among other harmful consequences. Moreover, in certain cases photogenotoxicity and photocarcinogenic risks should be taken into account depending on the specific compound and treatment conditions [3].

Conventional psoralen derivatives, although effective in particular cases, have photoactivation dependency and the ability to undergo harmful photochemical reactions, which make the study of new molecular derivatives relevant. The aim of structural optimization is to determine those molecular properties which could retain pharmacological advantages and avoid negative DNA interaction and toxicity.

Earlier researches showed that modification of the structure of the psoralen molecule could lead to changes in the biological activity of this substance and in the ability of psoralens to bind to the DNA molecules. The review by Jamalis et al. described methods of synthesis and pharmacological properties of psoralen derivatives, while Buhimschi et al. proved that modification of substituents could significantly affect psoralen potency and DNA adduction [1,4].

One more way of evaluating possible structure analogs is computer-aided drug designing. Molecular docking is used to evaluate how certain molecules interact with proteins. Physicochemical parameters and predictions of ADMET profile could help to find drug-like compounds which have undesirable properties for the drug. But protein docking alone is not enough to prove that a compound has decreased phototoxicity since photochemical reaction should be assessed separately.

That is why the topic of this review is development of safer psoralen analogs using structural modification and molecular modeling.

MATERIALS AND METHODS

The current review has been generated based on information available in the literature about psoralen chemistry, photochemistry, pharmacological activity, modifications, phototoxicity and drug design. Relevant literature includes reviews of psoralen analogues, experimental studies of psoralen analogues and genotoxic effects of furocoumarins upon exposure to UVA.

Selection of literature was carried out on the basis of their relevance to the following areas of interest:

Chemical structure and pharmacology of psoralen.

Intercalation, photo-addition reactions and UVA phototoxicity.

Structure-activity relationship studies of substituted psoralen analogues.

Approaches for the modification of the psoralen structure.

Molecular docking and ADME/Tox predictions.

The presented evidence was categorized according to themes in order to discover ways to create an analogue which is relatively safe. It was mainly focused on structural changes of psoralen structure at certain positions and possible application of computational screening for the purpose of selecting promising candidates.

A computational approach for the mentioned project can include the design of psoralen analogues through chemical drawing, assessment of physicochemical properties, molecular docking with selected target protein and in silico ADMET study. It should be noted that the results should be treated as computational evidence and not as biological proof of reduced toxicity or efficiency.

STRUCTURE–ACTIVITY RELATIONSHIP (SAR)

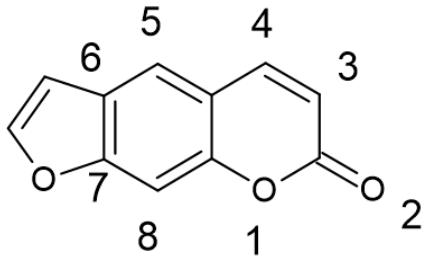


Figure 1:2D structure of Psoralen

Studies in the field of structure-activity relationships explore the impact of structural modifications on biological activity, drug-target interactions, and physicochemical properties. In psoralen

chemistry, the fusion of furocoumarin ring systems is related to the DNA intercalating and photochemical properties of the compounds. Hence, the modification needs to take into account both pharmacologically desired and undesirable photobiological properties [1,4].

Significance of the Psoralen Scaffold

The planar and conjugated tricyclic molecule structure gives psoralens their ability to interact with DNA. The photochemical properties give psoralens the ability to form DNA adducts upon the absorption of UVA radiation. Significant alterations in the planarity, conjugation or absorption of light can have an impact on such interactions, but the nature and extent of this impact need to be determined.

The psoralen scaffold is therefore an ideal place to start in designing analogues. Modification needs to be evaluated not only for the expected protein binding interactions but also for the ultraviolet-visible light absorption and DNA interactions.

Substitution at the C5 Position

C5 substitution could be considered an option for studying the effects of modifications on the electronic and physicochemical properties of psoralen analogues. Possible functional groups for substitutions could be hydroxyl, methoxy, ethoxy, amino, cyano, and others.

These alterations might affect the hydrogen-bonding ability, electron distribution, molecular polarity, lipophilicity, and biological properties. Nevertheless, the presence of a certain substituent does not necessarily imply less phototoxicity. In order to understand the effect of substitution on photochemical reactivity and biological activity, it needs to be investigated separately for each compound.

Substitution at the C8 Position

C8 substitution is another method of investigation of the correlation between the molecular structure and biological properties. Examples of such substitutions in psoralen derivatives are methoxy and amino groups; however, other functional groups could also be studied as computational design hypotheses.

The analysis of C5- and C8-substituted analogues could help to understand the role of the substitution position in molecular recognition, physicochemical properties, and predicted ADMET behaviour. Comparison of a matched pair, where only the position of substitution changes, could be especially useful for interpreting computational data.

Modification of Functional Groups

The addition of polar or ionizable functional groups could affect aqueous solubility, hydrogen-bonding ability and distributive properties. Groups like hydroxyl, amino, amide, and other similar

functional groups could be studied under analogues library.

The modifications would allow certain physicochemical properties to be enhanced; however, increased polarity is not a guarantee of decreased phototoxicity. The analogues should be studied on their own in order to examine their absorption behavior, phototoxicity, interaction with DNA and biological activity.

Heterocyclic and Aromatic Modification

The introduction of heterocyclic functional groups such as pyridine, pyrimidine, imidazole, triazole, and others, could allow the modification of molecular recognition and physicochemical properties. Aromatic functional groups and linkers could affect the molecular size, flexibility and lipophilicity.

Such modifications need to be studied carefully, as the increase of conjugation or changes of electronic structure could affect ultraviolet absorption and excited states behavior. Novelty of the structure cannot be considered as proof of enhanced safety.

DNA Binding and Phototoxicity

Phototoxicity linked to psoralens is related to light-dependent DNA photochemistry. DNA modifications such as adduct formation and cross-linking can cause problems in the normal functioning of cells. Buhimschi et al. showed that higher DNA-binding capacity was linked to greater cytotoxic effects of many tested psoralens [4].

This fact underlines the necessity to take into account another design feature: the greater effect could go hand in hand with increased DNA binding and thus should not be considered a sign of safer molecules.

PHARMACOLOGICAL ACTIVITY

Psoralen and its analogues have been evaluated for various pharmacological effects, which include photosensitizing, antiproliferative and other biological properties. The pharmacological effects are determined by the structural characteristics of the compounds, biological systems, and exposure to UVA radiation in the case of most practical uses [1,2].

Psoralen-UVA Reaction

The reaction of psoralen with DNA and absorption of the UVA radiation by the compound leads to its excitation. Subsequently, the excited molecule reacts with pyrimidine bases resulting in photo adduct formation. The further reactions result in DNA interstrand crosslinking, which leads to the interference with DNA replication and transcription.

This process is an important part of the mechanism of action of psoralen-UVA therapy; at the same time, it is responsible for its phototoxic and photogenotoxic properties. In this connection, the

absence of phototoxic properties cannot be confirmed simply by the calculation of the favorable docking score of the compound towards a protein.

Phototoxicity Issues

The photogenicity and photo irritation of furocoumarins, such as 8-methoxypsoralen and 5-methoxypsoralen have been shown after UVA exposure. This issue has been addressed in the paper by Irizar et al. [3].

Derivatives that may present lower risk should therefore be evaluated for photobiological properties such as their capacity to absorb light, photochemical reactions, DNA photoadducts formation and cellular toxicity in presence and absence of irradiation.

Biological Properties without Activation by UVA

One interesting issue to address is whether the selected psoralen derivatives can have biological properties independent from UVA irradiation. This property may be investigated during design of derivative with target protein in mind.

But experimental proof of biological properties without UVA irradiation will need to be demonstrated. Molecular docking may show possible interaction with the protein, but not its target inhibition, cell activity and lack of photoactivation.

Antiproliferative Properties and Target-Based Study

Biological properties of selected psoralen derivatives can be studied with respect to proteins involved in cell proliferation. One such protein is epidermal growth factor receptor (EGFR).

The structure of EGFR kinase domain with PDB ID 1M14 may be used as a target structure for docking study [5]. However, EGFR as the docking target is a hypothesis in a particular study and cannot be considered evidence of psoralen inhibition or EGFR inhibition leading to lower phototoxicity.

MOLECULAR DOCKING AND COMPUTATIONAL DESIGN

Computer-assisted drug design is very helpful in prioritizing candidate compounds for further research through molecular modeling, physicochemical analysis, and computing. In developing psoralen analogues, these techniques can prove to be very handy while making structural comparisons of the molecules which need further experimental research.

Molecular Modeling and Analogue Development

It is possible to generate a library of psoralen analogues through introduction of specific substituents on the scaffold. It must be ensured that all structures have the correct connectivity between the atoms, appropriate substitution site, stereospecific requirement, wherever applicable, and appropriate bonding.

It is possible to include in the library monosubstituted, disubstituted analogues and selected heterocyclic derivatives.

Molecular Docking

This method allows for estimating the possible positions of a ligand inside a protein-binding site and assessing the interaction potential via a scoring function. Psoralen analogue ligands could be docked against the chosen EGFR kinase domain structure, with the PDB ID of 1M14, after preparing both the protein and the ligands [5].

This process could involve taking into account docking score values, hydrogen bonding, hydrophobic contacts, aromatic interactions, and the position of each ligand inside the binding pocket. A known co-crystallized ligand may serve as an example to check the docking protocol.

It should be noted that docking scores are not experimental measures of binding affinity or biological activity of the ligand. The target itself must also have biological rationale behind its selection.

Drug-Likeness and Physicochemical Profiling

Physicochemical profiling may be helpful in the detection of potentially problematic compounds prior to further analysis. Such parameters could be, for example, molecular weight, predicted lipophilicity, number of hydrogen bond donors and acceptors, topological polar surface area and rotatable bonds.

Such parameters might affect solubility, permeability and suitability of the compounds under consideration. However, drug-likeness predictions do not involve direct testing of phototoxicity.

ADMET and Toxicity Predictions

In-silico ADMET predictors could give preliminary predictions regarding absorption, distribution, metabolism, excretion and some aspects of toxicity. These predictions can be used to analyze candidate molecules and detect potentially problematic traits.

For the present research direction, the general toxicity prediction must be separated from the phototoxicity prediction. The compound having good ADMET properties might absorb UVA light and generate DNA photoadducts.

Integrated Candidate Prioritization

The integrated computational protocol might include:

Design and validation of the chemical structures.

Calculation of physiochemical and drug-like properties.

Assessment of predicted biological activities.

Preparation of the chosen protein target and docking analysis.

Prediction and analysis of the interaction between ligands and proteins.

Comparison of ADMET and toxicity predictions.

Prioritization of candidates based on phototoxicity and biological assessment.

It is important to take into account several different criteria instead of choosing one compound because of its good docking score.

RESULTS AND DISCUSSION

It follows from the analyzed scientific literature that the structure of psoralen as a biologically active furocoumarin possesses considerable pharmaceutical significance owing to its photochemical properties, which determine both pharmacological applications of the compound and the possibility of side phototoxic and photogenotoxic effects [1–4].

The analysis of scientific studies concerning psoralen derivatives reveals that structural modification can change both biological activity and the interaction with DNA. In particular, according to the study by Buhimschi et al., some changes in the structure of psoralen can affect its cytotoxicity and DNA-adduct formation [4]. This provides an idea for the development of analogues, but it also makes it evident that enhanced biological activity cannot always be associated with higher safety.

C5 and C8 substitution, functional group modification and heterocyclic substitution appear as possible variants of analogue structure investigation. It is a hypothesis that can be tested unless proven experimentally.

The application of computational techniques can assist in the comparison of the candidate structures prior to synthesis and biological evaluation. Docking can explore potential binding between the molecule and a chosen protein target, whereas physicochemical and ADMET analysis can reveal potentially unfavorable molecular properties. In the current project, EGFR structure 1M14 constitutes a potential target for examining the interaction with a ligand [5]. The appropriateness of the molecule for the biological goal must be considered independently from the phototoxicity issue.

One of the main problems is that neither docking, nor traditional ADMET evaluation, adequately reflects the photo reactivity of psoralens analogs. The diminished phototoxicity needs to be studied via the appropriate tests that involve both light-dependent and light-independent assays, including the comparative assessment of cellular response to UVA irradiation and DNA photo adduct formation.

Therefore, the suggested workflow needs to be regarded as the candidate screening procedure. It is necessary to combine the evidence of biological activity and the decreased phototoxicity for finding a safer molecule.

CONCLUSION

Psoralen represents an important pharmacological scaffold already proven to have therapeutic uses in photochemotherapy and still holds possibilities for optimization. Nonetheless, the photochemistry of psoralen under UVA light exposure may result in undesired phototoxic and photogenotoxic consequences and, therefore, requires the study of more suitable derivatives.

The structural changes in selected sites of the psoralen scaffold such as C5 and C8 positions, as well as the introduction of functional groups and heterocycles, represent an effective method for the exploration of new properties of the compound. Computer-aided drug design may facilitate this procedure via molecular modeling, docking, drug-likeness and ADMET analysis.

In regard to the current project, these approaches could help identify priority candidate psoralen analogs for further studies. However, a good docking score or a satisfactory ADMET prediction would not guarantee that a molecule will have lower phototoxicity or activity irrespective of the exposure to UVA radiation.

The combination of structure-activity relationship analysis, computational screening and experiment could prove to be a logical approach to selecting psoralen derivatives with possibly enhanced safety and activity profiles.

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