ECMC-P 2025 Conference
The 1st International Electronic Conference on Medicinal Chemistry and Pharmaceutics
01–30 November 2025 | Online
MDPI

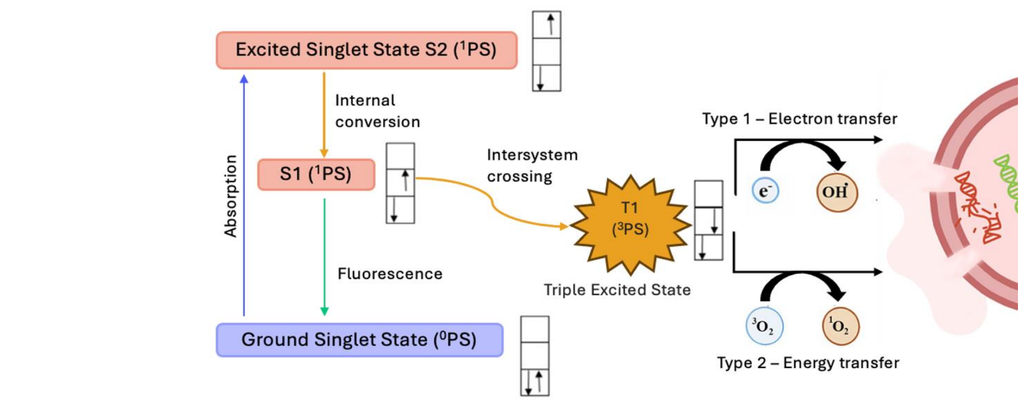
Evaluation of Curcumin and Its Derivatives as Photosensitizers for Antibacterial Photodynamic Therapy through an In-House Irradiation Assay

Dafnomili Sofia[1], Sagnou Marina[1,2], Kythreoti Georgia[1]
[1] Deree-The American College of Greece, Department of Science and Mathematics, Athens, Greece
[2] National Centre for Scientific Research "Demokritos", Institute of Biosciences and Applications, Athens, Greece

INTRODUCTION & AIM

Antimicrobial resistance (AMR) is a growing global health threat, with an overwhelmingly high number of deaths attributed to drug-resistant infections [1]. Antimicrobial photodynamic therapy (aPDT) offers a promising non-antibiotic alternative that combines a photosensitizer (PS), visible light, and molecular oxygen to generate reactive oxygen species (ROS) that kill bacteria [2]. Curcumin, a natural polyphenol contained in turmeric, shows potential as a PS due to its ROS-generating capacity when irradiated with blue light. However, limitations such as poor solubility, photoinstability, and low affinity for bacterial membranes reduce its clinical utility [3]. This project explores whether chemical modifications to curcumin can enhance its antibacterial PDT performance. aPDT involves excitation of the PS to a higher energy state, followed by intersystem crossing to a triplet state. ROS can then be generated either through electron transfer (Type I) or energy transfer to molecular oxygen (Type II), leading to damaged microbial structures such as membranes, proteins, and nucleic acids, resulting in cell death [4].

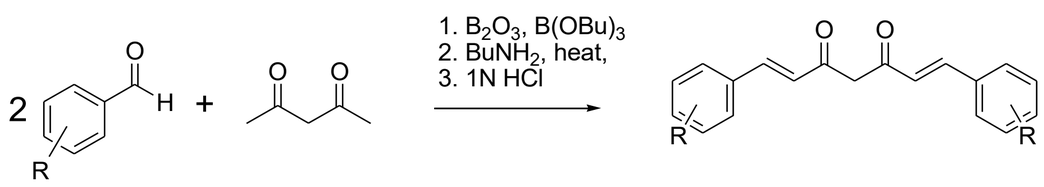
Figure 1
Jablonski Diagram: The Photochemical Mechanism of Action in Antimicrobial Photodynamic Therapy



METHOD

Compounds were synthesized via a three-step Pabon-based method involving boron-mediated protection of 2,4-pentanedione, aldol condensation with substituted benzaldehydes, and deprotection. Designed analogues aimed to enhance solubility, photostability, and light absorption.

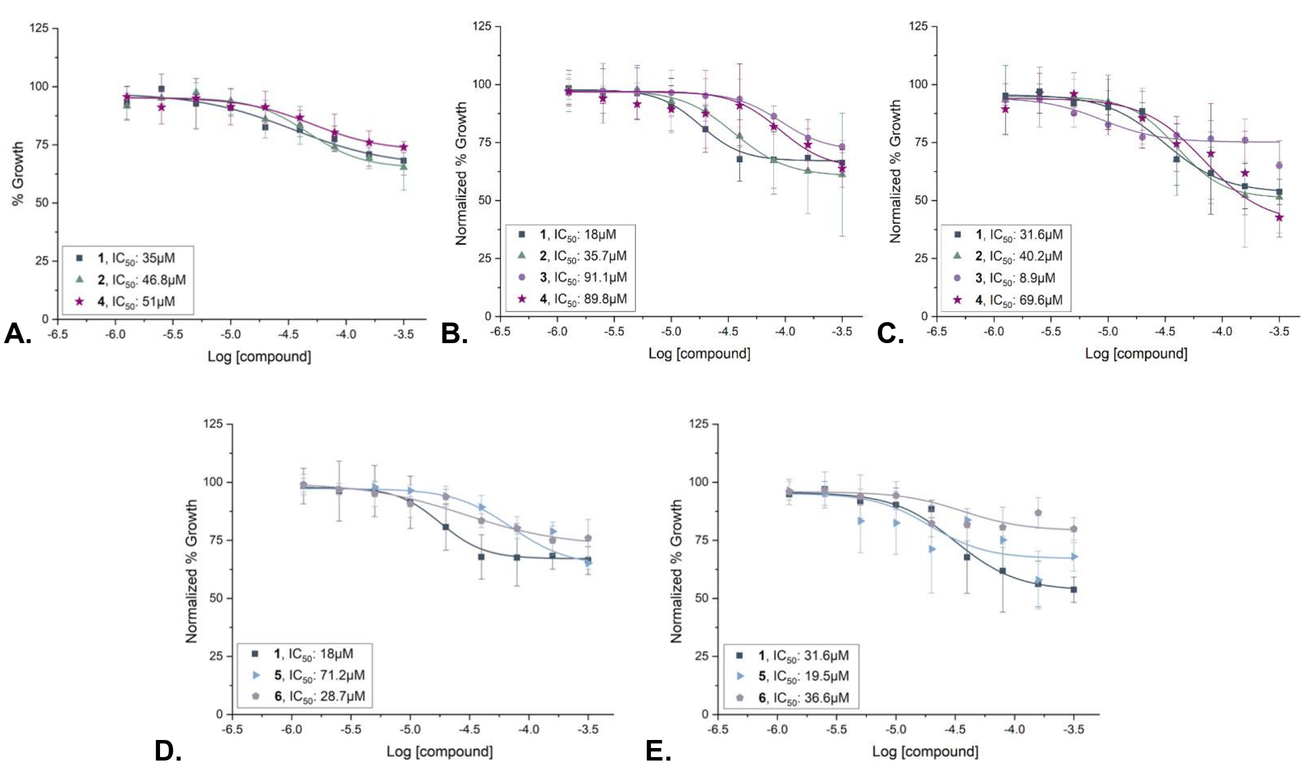
Figure 2
General Synthetic Route for Curcumin Analogues



Photophysical characterization was performed using UV-Vis spectroscopy (300–700 nm) in DMSO to evaluate light absorption properties. Photodynamic activity was assessed by exposing treated samples (0.3 mM to 0.0012 mM) to a 470 nm blue LED for 3 hours at an intensity of ~10 mW/cm². Bacterial growth inhibition potencies of tested PSs were determined via a 96-well format microdilution assay with controls for dark, light-only, DMSO vehicle, and growth inhibition. Statistically significant differences between irradiated and dark controls were assessed with paired t-tests for each tested concentration of each compound across biological repetitions.

RESULTS & DISCUSSION

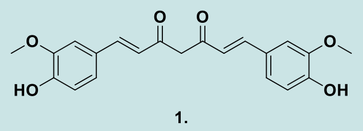
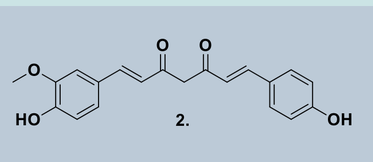
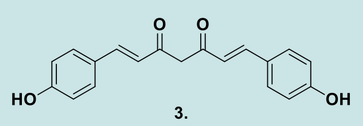
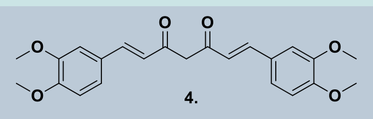
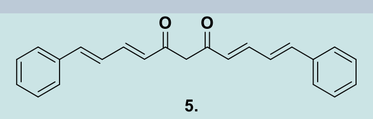
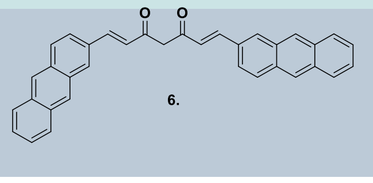
Figure 3
Dose Response Curves of Selected Analogues



Dose Response curves of analogues as compared to **curcumin** (**1**). **A**. *E. coli* percent growth after treatment with activated **1**, **2** and **4** (active). **B.** *P. aeruginosa* and **C.** *S. aureus* percent growth after treatment with activated **1**, **2** , **3** and **4**. **D**. *P. aeruginosa* and **E**. *S. aureus* percent growth after treatment with activated **1**, **5** , and **6**. IC_{50} values are also presented. These data illustrate how structural modifications affect bacterial susceptibility, with native **curcumin** (**1**) performing consistently across all species, while π-extended analogues showed selective or diminished efficacy.

Activity tracks a balance between conjugation and polarity. Retaining the β-diketone and phenolic functionalities is important: capping –OHs (**4**) depresses activity, while removing methoxy groups (**2**, **3**) can preserve efficacy (**2**) and lower IC_{50} against *E.*coli and *S. aureus* but also plateaus (**3**), consistent with aggregation at higher doses. π-Extension (**5**, **6**) red-shifts absorption slightly yet increases hydrophobicity, possibly undermining uptake, abolishing activity in *E. coli* and yielding species-selective effects (**5** for *S. aureus*) improving curcumin's (**1**) IC_{50} for maximum effect. Overall, the best performance is observed from moderate hydrophobicity with accessible phenols.

Table 1
Comparative Summary of Curcumin and Analogues in Photodynamic Efficacy

Compound	Structure	*E.coli*	*P. aeruginosa*	*S. aureus*
1 curcumin	 1.	IC_{50}: 35μM E_{max}=30%	IC_{50}: 18μM E_{max}=33%	IC_{50}: 31.6μM E_{max}=45%
2	 2.	IC_{50}: 46.8μM E_{max}=33%	IC_{50}: 35.7μM E_{max}=38%	IC_{50}: 40.2μM E_{max}=47%
3	 3.	IC_{50}: 18.5μM E_{max}=13%	IC_{50}: 91.1μM E_{max}=25%	IC_{50}: 8.9μM E_{max}=20%
4	 4.	IC_{50}: 51μM E_{max}=23%	IC_{50}: 89.8μM E_{max}=38%	IC_{50}: 69.6μM E_{max}=36%
5	 5.	Not active	IC_{50}: 71.2μM E_{max}=36%	IC_{50}: 19.5μM E_{max}=40%
6	 6.	Not active	IC_{50}: 28.7μM E_{max}=22%	IC_{50}: 36.6μM E_{max}=20%

This table presents the structural differences and photodynamic antibacterial activity of curcumin (**1**) and its five analogues (**2**–**6**). Key metrics include IC_{50} values and E_{max} (maximum inhibition), across three bacterial strains (*E. coli, P. aeruginosa, S. aureus*).

CONCLUSION

Most compounds showed minimal dark toxicity, confirming light-dependent antibacterial effects. Structural modifications of curcumin (**1**) markedly affected both photophysical and biological properties: removing methoxy groups (**2, 3**) slightly reduced efficacy, while full methylation (**4**) diminished activity. **3** exhibited the lowest IC_{50} against *S. aureus* but displayed a small effect, possibly due to aggregation issues. Extending π-conjugation (**5**, **6**) produced slightly red-shifted absorption spectra (data not shown), confirming successful spectral tuning for activation at selected wavelengths. However, these analogues did not consistently enhance antibacterial performance, implying that absorption alone is insufficient and factors like membrane affinity, cellular uptake, and ROS yield are also critical. *P. aeruginosa* was generally more resistant, except for **6**, which retained curcumin's activity. *S. aureus* was the most susceptible, where improved IC_{50} was observed (**5**). Both suggesting potential for selective applications. Overall, **1** remains a reliable reference photosensitizer, while its analogues provide target-specific advantages. Future efforts will focus on optimizing the balance between photophysical efficiency and biological delivery, potentially through targeted or conjugated systems.

REFERENCES

1. Sirwan, K. A., et al., *Journal of Medicine Surgery and Public Health,* **2024**., 100081–100081.
2. Lima, E., et al., *Molecules*, **2023,** 28(13), 5092.
3. Wang, X., et al., *Frontiers in Immunology*, **2023,** 14.
4. Zhang, C., et al., *National Science Review*, **2024,** 11(9).