Graduate Students, Medical, Biomedical and Health Sciences

# Development of Novel Chalcone Analogs as Potential Multi-Targeted Therapies for Castration-Resistant Prostate Cancer


**Ola Hussein[1], Feras Alali[1], Ala-Eddin Al Mustafa[2,3], Ashraf Khalil[1]**

[1]College of Pharmacy, [2]College of Medicine and [3]Biomedical Research Center, QU Health, Qatar University, Doha, Qatar

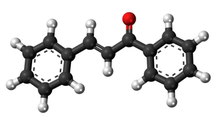

## Background

- Prostate cancer (PCa) is the second most frequently diagnosed malignancy and a leading cause of cancer-related mortality in men globally
- Despite the initial improvement to hormone targeted therapy, most patients ultimately develop resistance
- Castration resistant prostate cancer is associated with poor prognosis and available therapies cannot prolong survival for more than 5 months.
- Chalcones (C6-C3-C6) are highly attractive scaffolds that posses a wide variety of biological activities

## Objectives

1. Design, synthesize and elucidate the structure of novel chalcone analogs
2. Evaluate their in-vitro anticancer activity and in-ovo antiangiogenic effect

## Methods



**Design of Novel Chalcones**
(Confirm Novelty using SciFinder)

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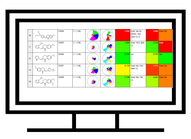
***In Silico* ADMET Screening**
(Swiss ADME and ADMET Predictor™)



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**Chemical Synthesis**
(Using Claisen-Schmidt condensation reaction)

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**Chemical Purification**
(Flash chromatography, recrystallization, prep-HPLC)

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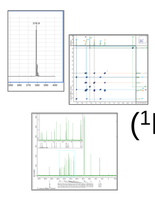

**Structure Elucidation**
([1]H and [13]C NMR, LCMS, elemental analysis, FT-IR)

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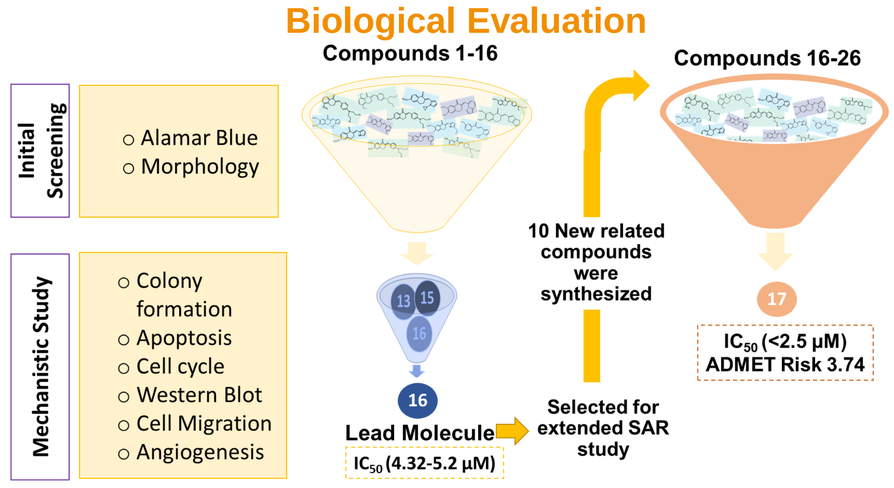
**Biological Evaluation**




## Results

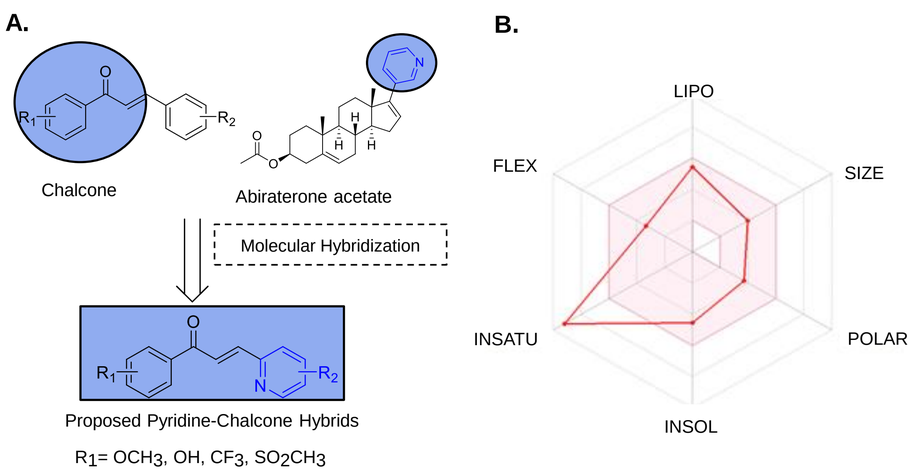



**Figure 1. The rationale for the design of pyridine-chalcone Hybrids (A) Predicted drug-likeness properties of compound 17 (B).**

## Results

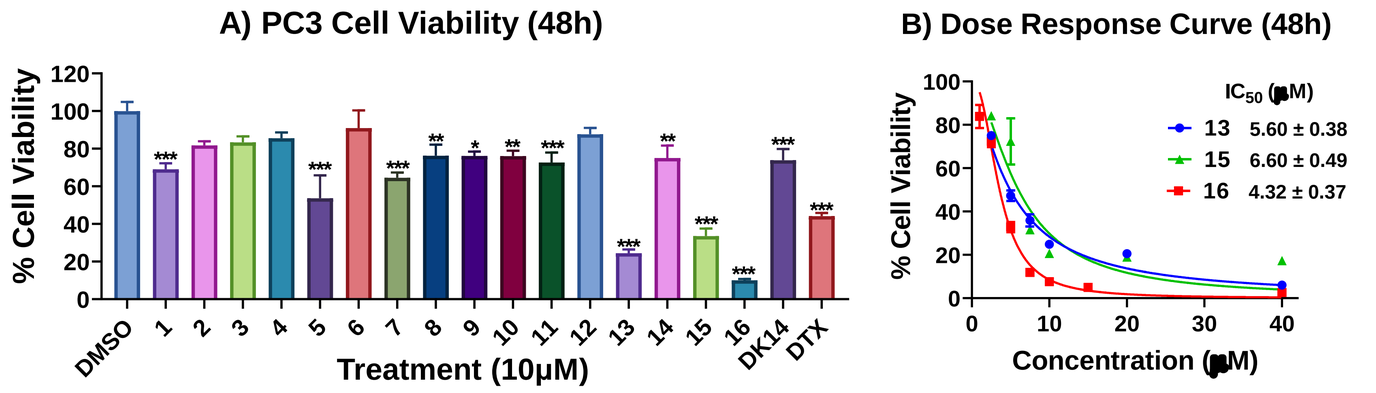



**Figure 2. Effect of compounds 1-16 on the cell viability of PC3. Values are expressed as mean ±SEM. *P < 0.01, **P < 0.001 vs. control (A). Dose response curve against PC3 for the most potent analogs (B).**

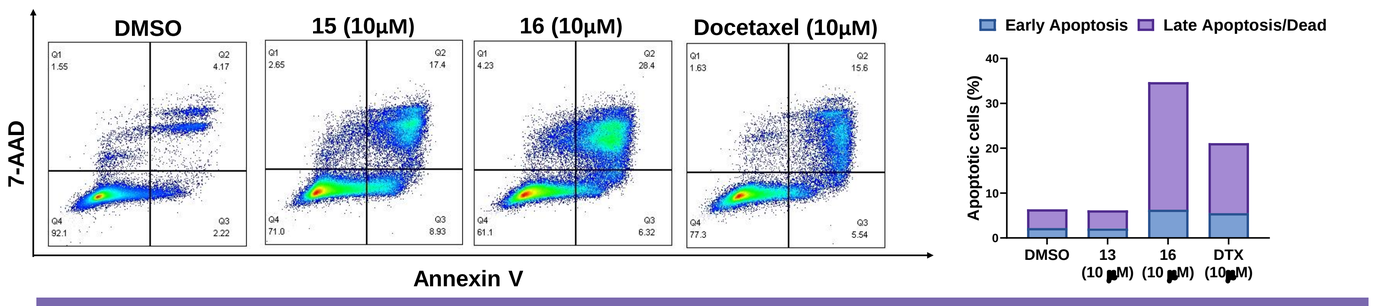



**Figure 3. Effect of compounds 15 and 16 on apoptosis of PC3 cells.**

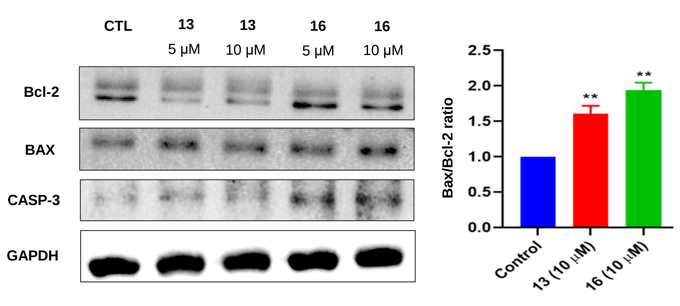



**Figure 4. Effect of compounds 13 and 16 on apoptosis related proteins in PC3 cells.**

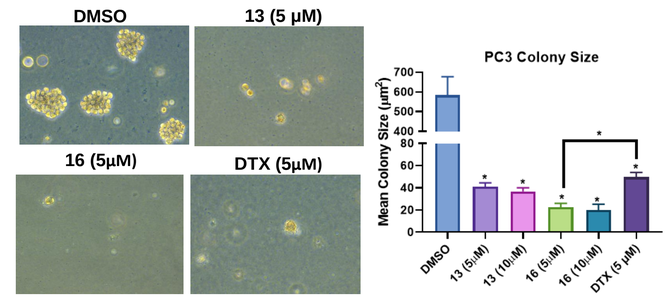



**Figure 5. Effect of compound 16 on soft agar colony formation of PC3 cells.**

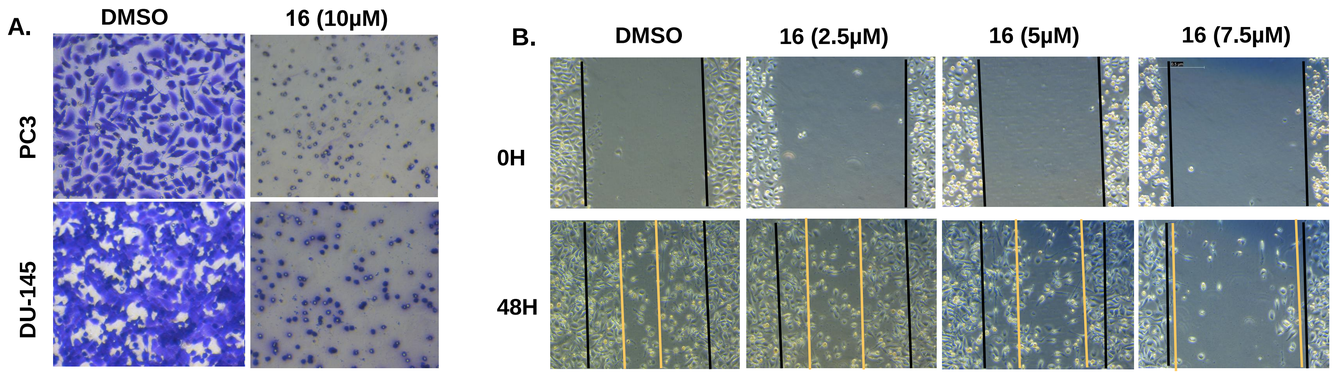



**Figure 6. Effect of compound 16 on trans well- (A) and wound healing- (B) migration assays.**

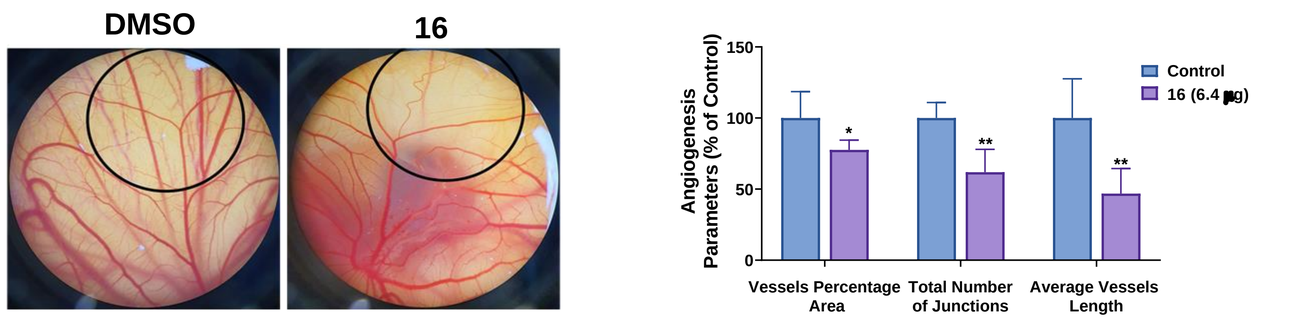



**Figure 7. Effect of compound 16 on Angiogenesis of the CAM of chicken embryos after 48 hours of treatment. The encircled zone marks the treated area**

## Conclusion

- Twenty-six novel chalcone analogs were designed and synthesized
- Compounds **13**, **15** and **16** showed potent antiproliferative activities at low micromolar levels with $IC_{50}$ values ranging between 4.3 and 6.6 µM against PC3 and DU145 cell lines
- Compound **16** significantly inhibited colony formation, migration and angiogenesis and induced apoptosis

## Future Direction

- These results indicate that compound **16** could serve a potential promising lead molecule for the treatment of PCa and thus, further *in vivo* studies are warranted.

## Acknowledgement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