Graduate Students, Medical, Biomedical and Health Sciences

Design, Synthesis and Biological Evaluation of Novel Chalcone Analogs as Potential Therapeutic Agents for Prostate Cancer

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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 tetralone-based chalcones
2. Evaluate their in-vitro anticancer activity and in-ovo antiangiogenic effect

Methods

Synthesis of novel Chalcones

(Using Claisen-Schmidt condensation reaction)

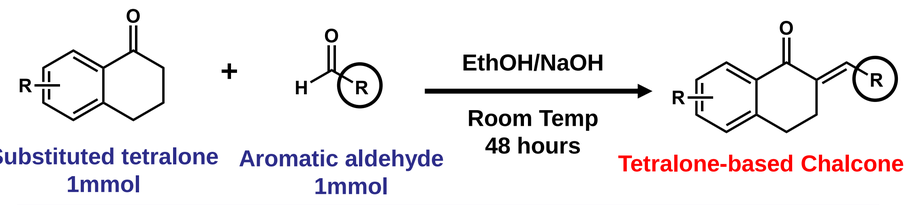


Figure 1: Tetralone-based chalcone synthetic scheme

Chemical purification
(column chromatography or recrystallization)

Structure Elucidation
(1H and 13C NMR and LCMS)

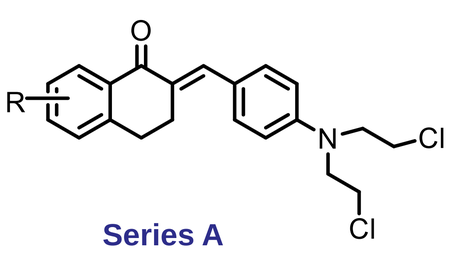
Biological Evaluation

Initial Screening
- 20 Analogs
- 4 Cell lines
  - Alamar Blue
  - Morphology

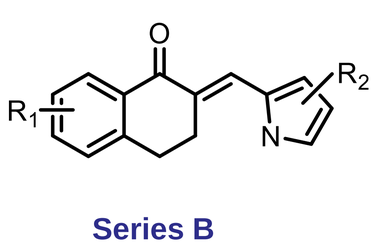
Mechanistic Study
- 3 Analogs + positive control (Docetaxel)
- 2 Cell lines
  - Colony formation
  - Apoptosis
  - Cell cycle
  - Western Blot
  - Cell Migration

***In Ovo*:**
- 5 analogs
- Chicken Embryos
  - Angiogenesis

Results- Chemistry



Series A



Series B

OH2	R 7-methoxy	
OH3	R 6,7-dimethoxy	
OH4	R 6-methoxy	
OH12	R 5,8-dimethoxy	
OH13	R 7-nitro	
OH6	R2 1-H	
OH5	R1 6-methoxy;	R2 1-cycloproyl
OH8	R1 6,7-dimethoxy;	R2 1-cycloproyl
OH9	R1 6,7-dimethoxy;	R2 5-ethyl

Figure 2: Chemical structures of selected tetralone analogs

Results-Biological Activity

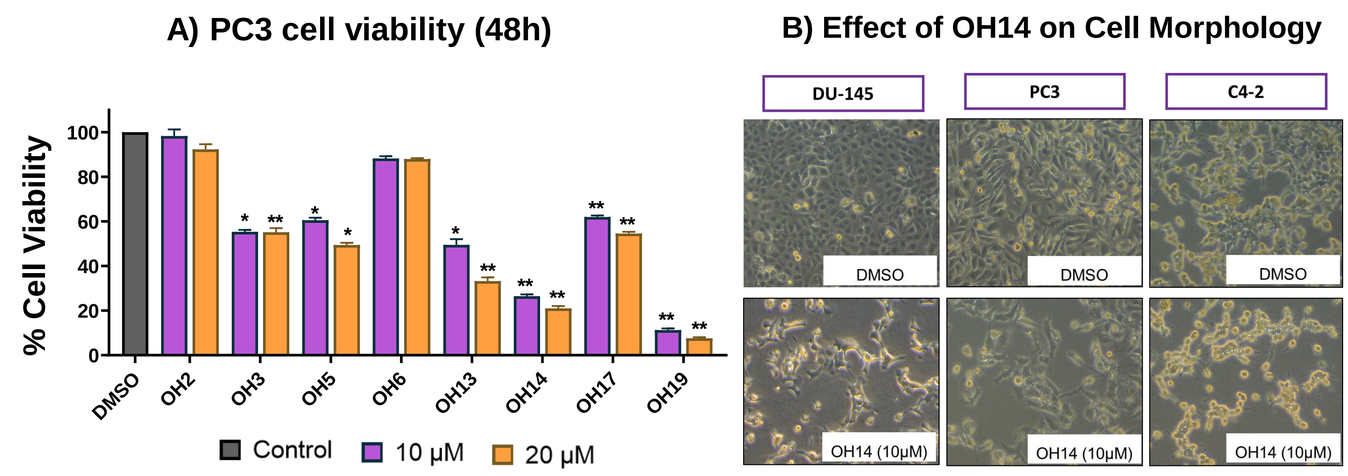


Figure 3: Effect of the compounds on cell viability of PC3 (A) and cell morphology of PCa cell lines(D). Values are expressed as mean ±SEM (n=2x4).*P < 0.01, **P < 0.001 vs. control.

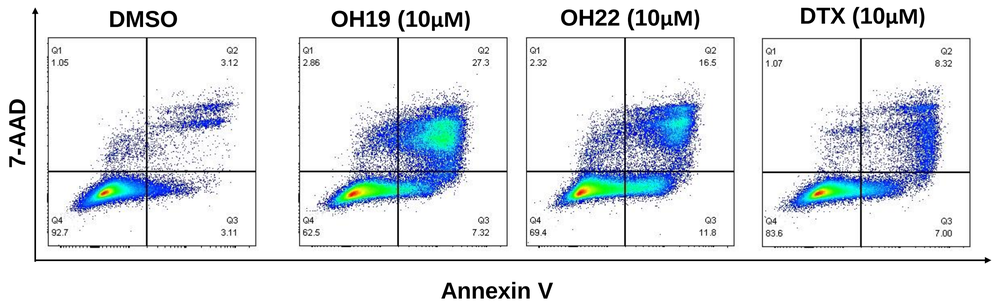


Figure 4: Effect of compounds OH19 and OH22 on apoptosis

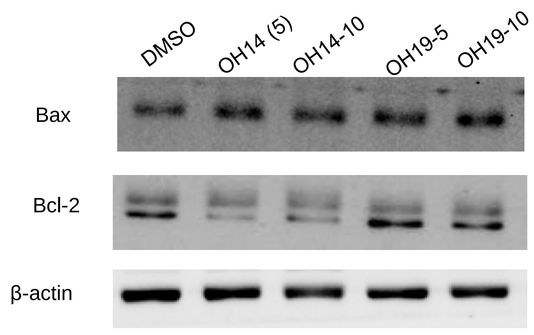


Figure 5: Effect of OH14 and OH19 on apoptosis related proteins in PC3

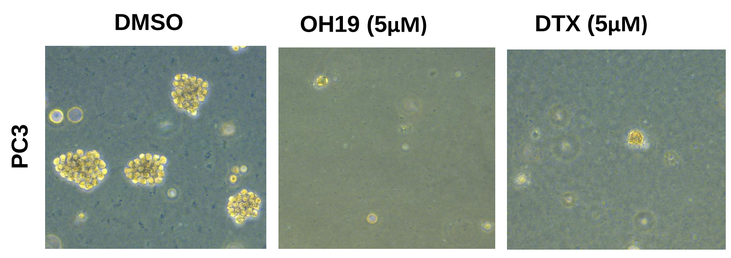


Figure 6: Effect of compound OH19 on soft agar colony formation

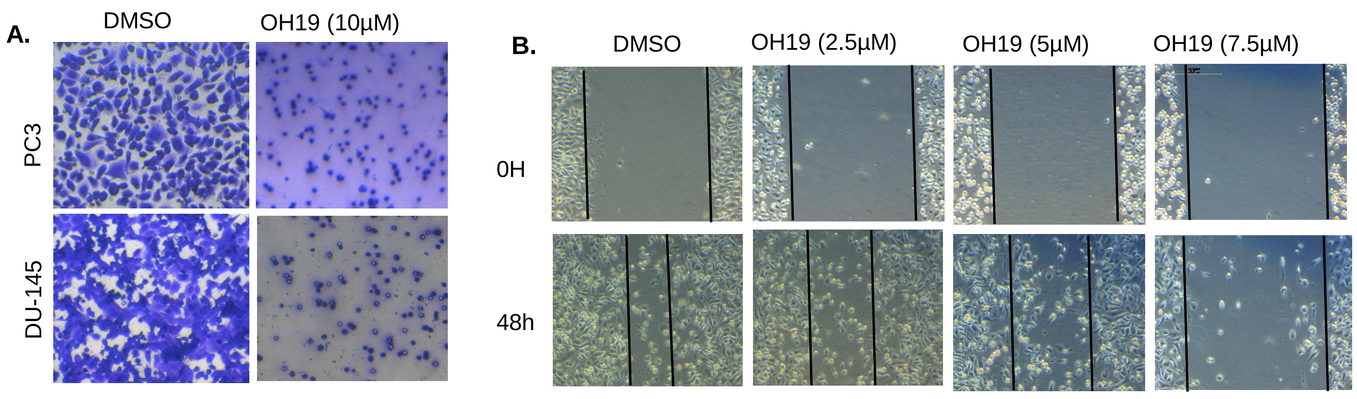
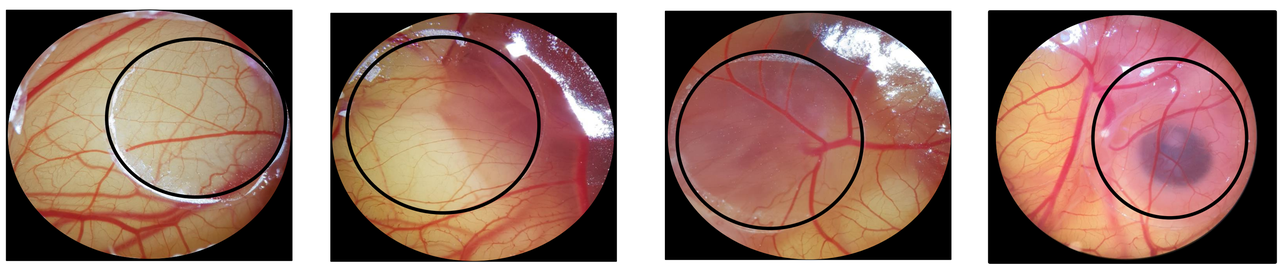


Figure 3: Effect of OH19 on trans well- (A) and wound healing- migration assays



Control (DMSO) **OH5 (10µM)** **OH3 (10µM)** **OH19 (10µM)**

Figure 6: Effect of compounds OH5, OH3, and OH19 on angiogenesis after 48 hours of treatment. The encircled zone marks the treated area.

Conclusion

- Twenty novel tetralone-based chalcones were designed and synthesized
- Compounds OH14, OH19 and OH22 showed potent antiproliferative activities at low micromolar levels with IC50 values ranging between 4.4 and 10µM against PC3 and DU145 cell lines
- Compound OH19 significantly inhibited colony formation, migration and angiogenesis and induced apoptosis
- These results indicate that OH19 could serve a potential promising lead molecule for the treatment of PCa and thus, further in-vitro and in-vivo testing is warranted.