Development of Novel Chalcone Analogs as Potential Multi-Targeted Therapies for Castration-Resistant 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 possess 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)
In Silico ADMET Screening (Swiss ADME and ADMET Predictor®)
Chemical Synthesis (Using Claisen-Schmidt condensation reaction)
Chemical Purification (Flash chromatography, recrystallization, prep-HPLC)
Structure Elucidation ($^1$H and $^13$$C$ NMR, LCMS, elemental analysis, FT-IR)
Biological Evaluation

Results

A) PC3 Cell Viability (48h)

B) Dose Response Curve (48h)

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 IC₅₀ 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 PCAs and thus, further in vivo studies are warranted.

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