Development of Potent Bakuchiol-derived Liver X Receptor Modulators

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I. Abstract

Liver X Receptors (LXRs) are ligand-dependent gene transcription factors that regulate lipid homeostatic pathways. The liver X receptors (LXRs) consists of two isoforms that share >70% sequence conservation in their ligand binding domain. Both isoforms LXRα and LXRβ are reported to be effective drug targets towards the treatment of various metabolic disorders. LXRα is most expressed in the liver and adipose tissue while LXRβ is expressed ubiquitously. LXR agonists are reported to facilitate reverse cholesterol transport (RCT), decreasing peripheral cholesterol accumulation. Due to their role as master lipid regulators, developing ligands that selectively target LXRs have been an emerging strategy to combat chemo-resistances cancer cells pose.

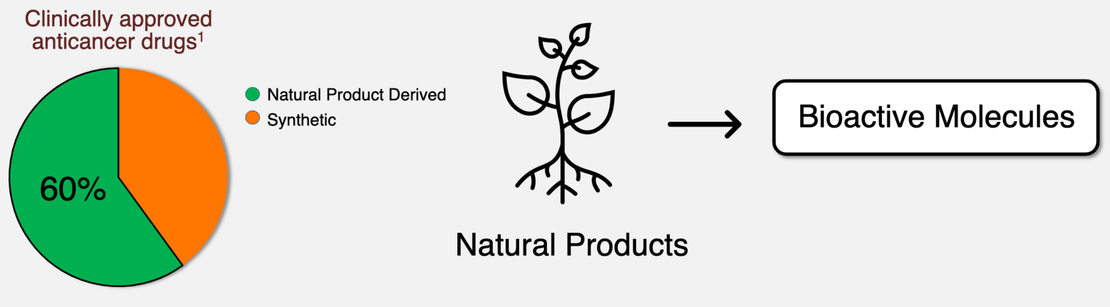
A library of bakuchiol derivatives was docked against reported LXR modulators using GOLD Dock. The structural binding of the highest scoring derivatives was then simulated using AMBER molecular dynamics suite. Our results strongly implicate higher binding affinity to LXRs than even endogenous oxysterols.

II. Introduction

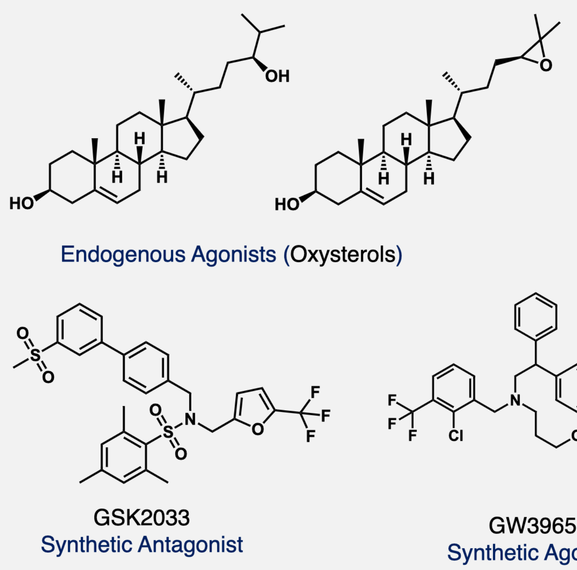
It is well-reported the link of high cholesterol levels to cancer prognosis.[1] The current generation LXR-targeting ligands were developed to treat atherosclerosis, but they have not been optimized towards cancer therapies. Furthermore, LXR targeting ligands have been assayed to be more selective and potent towards the LXRβ isoform.[2] The major drawback impeding the development of LXR agonists is the adverse effect of increased plasma triglyceride and hepatic steatosis. It has been reported that treating mice lacking LXRα with LXR dual agonists did not exhibit high triglyceride levels or hepatic steatosis, implicating LXRα activation is the main contributor to these adverse effects.[3] Therefore, our goal is the development of LXRα -selective inverse agonists or antagonists to interrogate the elusive activity of LXRα in cancer.

1) Newman, D. J, Cragg, G.M. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod. **75**, 311−335, 2012.
2) She J, Gu T, Pang X, Liu Y, Tang L and Zhou X (2022) Natural Products Targeting Liver X Receptors or Farnesoid X Receptor. Front. Pharmacol. 12:772435. doi: 10.3389/fphar.2021.772435
3) Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. Nat Rev Endocrinol. 2018;14(8):452-463. doi:10.1038/s41574-018-0037-x

III. Natural Product as Privileged Scaffolds



Current Known Liver X Receptor Ligands

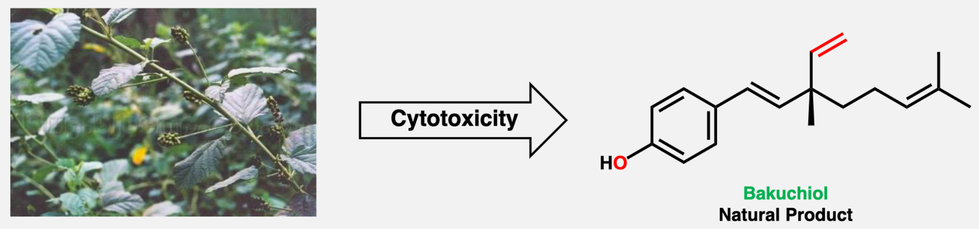


Target Genes

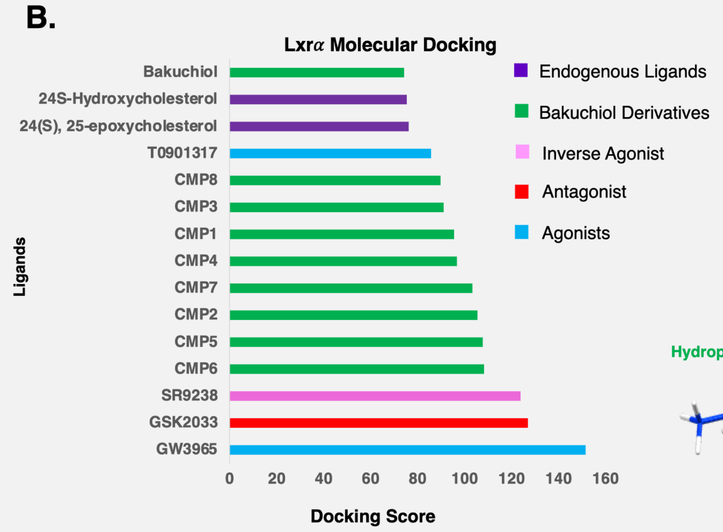
- **ABCA1**
- **SREBPc1**
- **CCR7**
- **ApoE**
- **IL-6**
- **Cyp7a1**

IV. Screening Approach

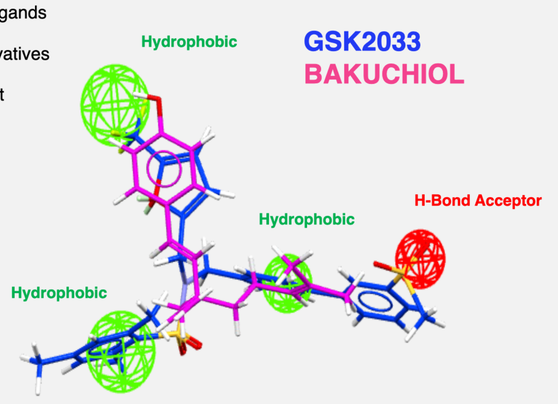
A. High Throughput Natural Product screen against SEM and Nalm06 (Acute Lymphoblastic Leukemia Models) **Assay**: *CellTiter Glo* (Cell Viability)



B.



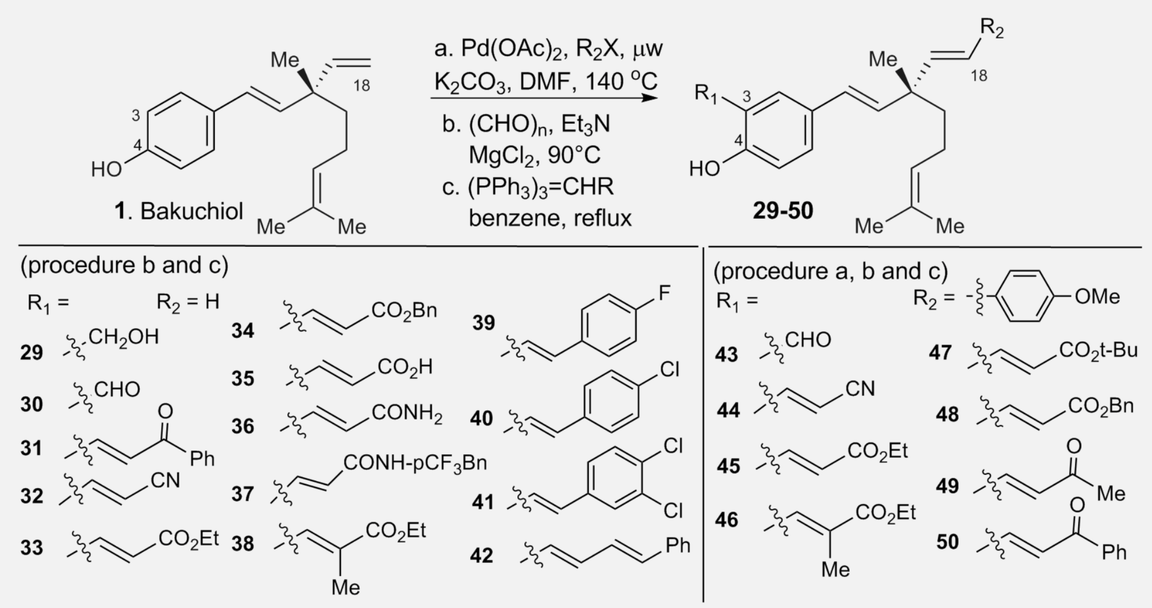
C. Pharmacophore Mapping



Figures **B** and **C** were obtained using GOLD Docking and Crossminer program by CCDC. Crystal structure of LXRα was using to perform *in-silco* docking studies. PDB: 3FC6

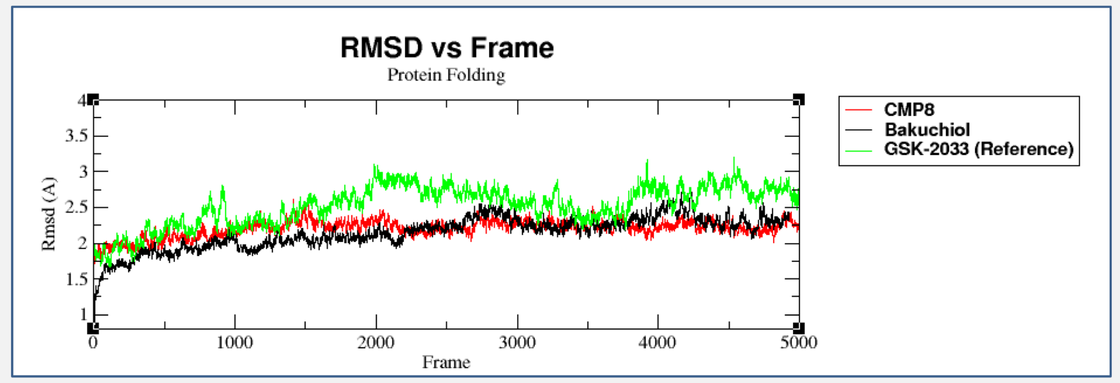
V. Synthesis of Bakuchiol Derivatives

Evaluation of C3 and C18 of the core system (yields = 60-98%)[5]

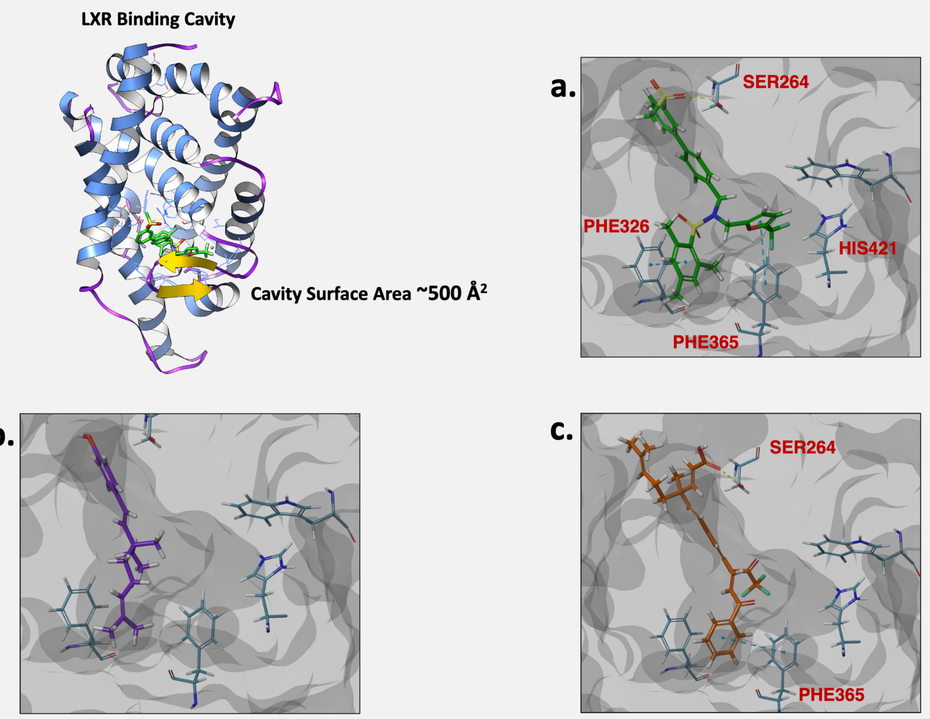


4) L.N. Gautam, T. Ling, W. Lang, F. Rivas, Anti-proliferative Evaluation of Monoterpene Derivatives against Leukemia, *European Journal of Medicinal Chemistry* (2016), doi: 10.1016/j.ejmech.2016.02.034.

IV. Molecular Dynamic Simulation



Representative protein unfolding during 25ns MD Simulation of LXRa complexed with ligamds. Simulations generated using AMBER molecular dynamic suite.



a. Predicted binding mode of GSK (green) to LXRa using GOLD Dock program. GSK forms Hbond with SER264 and pi-pi with PHE326, PHE365 **b.** Bakuchiol docked into LXRa. No H-Bond interactions were detected. **c.** CMP8 was a result of optimizations using the generated pharmacophore from screening.

V. Conclusion and Future Studies

A. We have identified bakuchiol as a lead scaffold effective against acute lymphoblastic leukemia cell lines.
B. Optimization of bakuchiol derivatives is guided by our modelled pharmacophore.
C. The derivatives synthesized will undergo an in-depth structure activity relationship study via cell viability assays for further derivatizations.

VI. Acknowledgements

We would like to take the Chemistry Department (**Louisiana State University, College of Science**) for technical and software support!