Synthesis and Biological Evaluation of Simple Baylis-Hillman Carboxylic Acid Esters as Potential Anticancer Agents

Yishu Zhang, Jake Gibbons, Skylar Hubbard, Tanner Schumacher, Zachary Gardner

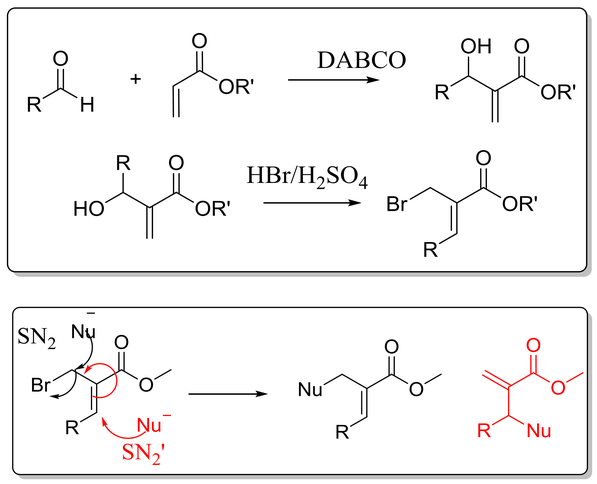
UMD
University of Minnesota Duluth
Driven to Discover

Introduction

Baylis Hillman (BH) reaction is important for C-C bond forming reactions in organic synthesis. Allyl alcohols can be synthesized readily by this reaction and these alcohols undergo nucleophilic rearrangement to provide wide range of useful synthons for organic and medicinal chemistry. We are interested in the development of new molecules based on BH reaction and we have initiated this project to explore novel functionalized allyl esters derived from BH reaction as potential anticancer agents.

We synthesized several carboxylic acids derived analogs of bromomethyl phenyl acrylate obtained from BH reaction. The allyl ester was further dihydroxylated using OsO_4. The synthesized molecules have been evaluated against several cancer cells including triple negative breast cancer cell line MDA-MB-231, and pancreatic cancer cell line MIAPaCa-2. These studies have indicated that several of the synthesized compounds show good cytotoxicity with EC_{50} values in the range of 3-73µM. Interestingly, the removal of electrophilic double bond in both compounds 2 and 4 reduced the biological activity.

Figure 1. Baylis Hillman reaction and nucleophilic rearrangement



Reaction Scheme

Figure 2: Synthesis of functionalized Baylis-Hillman based carboxylic esters

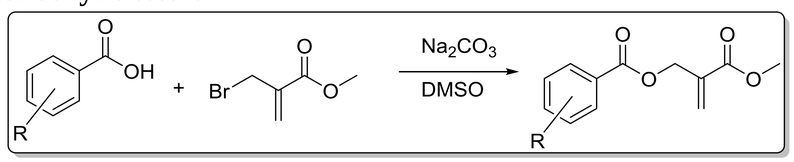


Figure 3: Synthesis of Baylis-Hillman diols

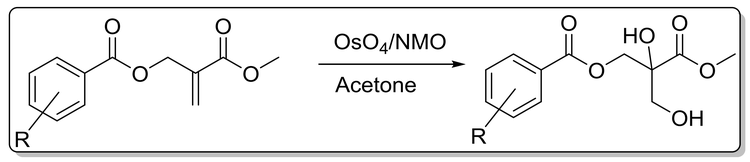
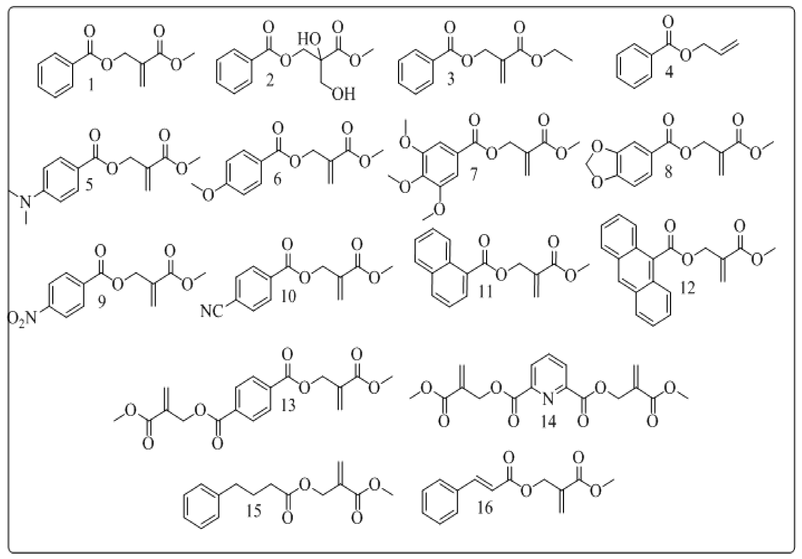
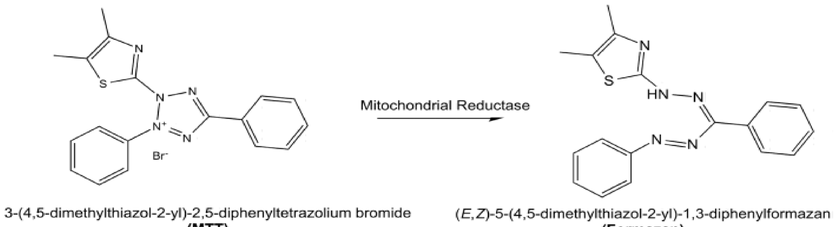


Figure 4: Baylis-Hillman esters and diols



In vitro Biology



3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide **(MTT)**

(*E*,*Z*)-5-(4,5-dimethylthiazol-2-yl)-1,3-diphenylformazan **(Formazan)**

- MTT assay is a standard cell proliferation assay
- In healthy cells, MTT is reduced by mitochondrial reductase to insoluble formazan compound.
- Formazan absorbs UV light at 570nm.
- Compounds are screened at numerous concentrations, and
- EC_{50} values are determined using graphpad prism software v6.0.

Cytotoxicity Studies

Table 1: EC_{50} values of respective compounds using MTT proliferation assay

EC_{50}±SEM (µM)		
Compound	MDA-MB-231	MIAPaCa-2
1	12.21±1.05	33.55±5.38
2	>100	>100
3	14.26±0.82	66.87±3.92
4	>100	>100
5	20.98±1.32	59.59±6.00
6	7.70± 0.36	28.5±4.12
7	8.14±0.88	22.14±3.34
8	11.42± 1.23	42.6±2.09
9	17.56± 0.63	24.07±3.34
10	11.82± 1.3	28.68±3.30
11	28.65±1.96	72.58±8.40
12	29.66±4.27	72.53±2.90
13	17.43±4.00	13.89±2.21
14	3.85±0.48	3.35±1.27
15	45.32±0.50	>100
16	41.47±4.35	64.36±4.27

Conclusion

- We have synthesized a series of structurally diverse Baylis-Hillman derived carboxylic esters.
- Structural diversity includes aromatic, non-aromatic, electron donating, and electron withdrawing substituents.
- We have found that by removing the electrophilicity of the double bond via dihydroxylation leads to a decreased biological activity.
- The mechanism of action as potential DNA alkylators will be confirmed in future studies.

References

1. Solono, L., Nelson, G., Ronayne, C., Leuth, E., Foxley, M., Jonnalagadda, SK., Gurrapu, S., Mereddy, VR., *Bioorg. Med. Chem. Lett.* **2015.** 25(24): 5777-80.
2. Tekkam, S.; Alam, M. A.; Jonnalagadda, S. C.; Mereddy, V. R. Chem. Comm. **2011**, 47, 3219.

Acknowledgements

- Dr. Venkatram Mereddy
- All graduate students
- UROP Funding
- The Department of Chemistry and Biochemistry