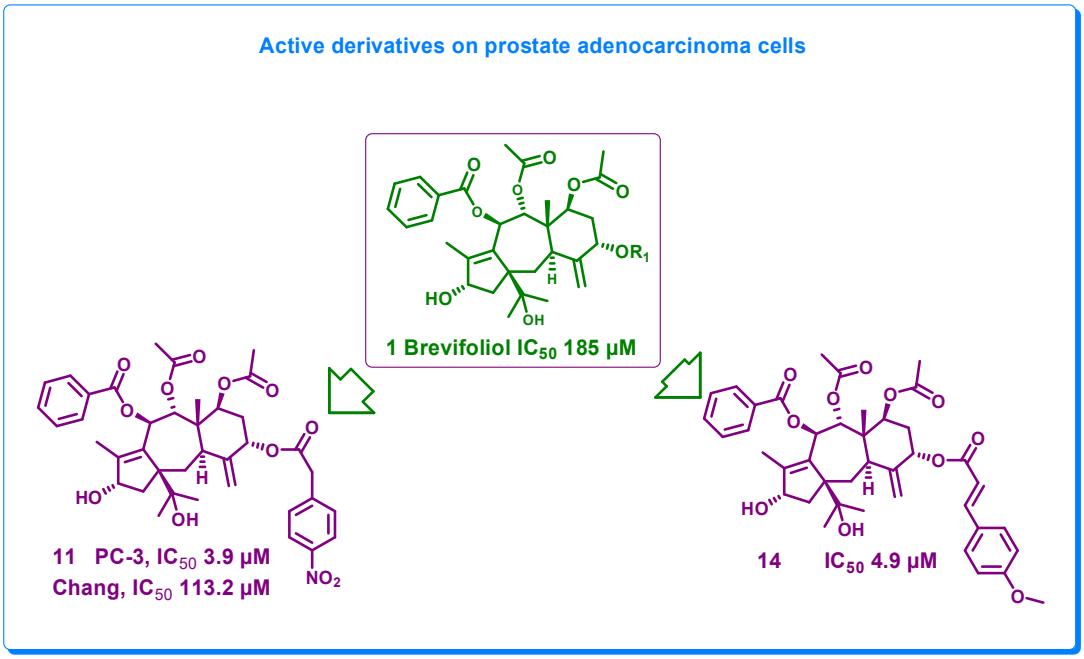
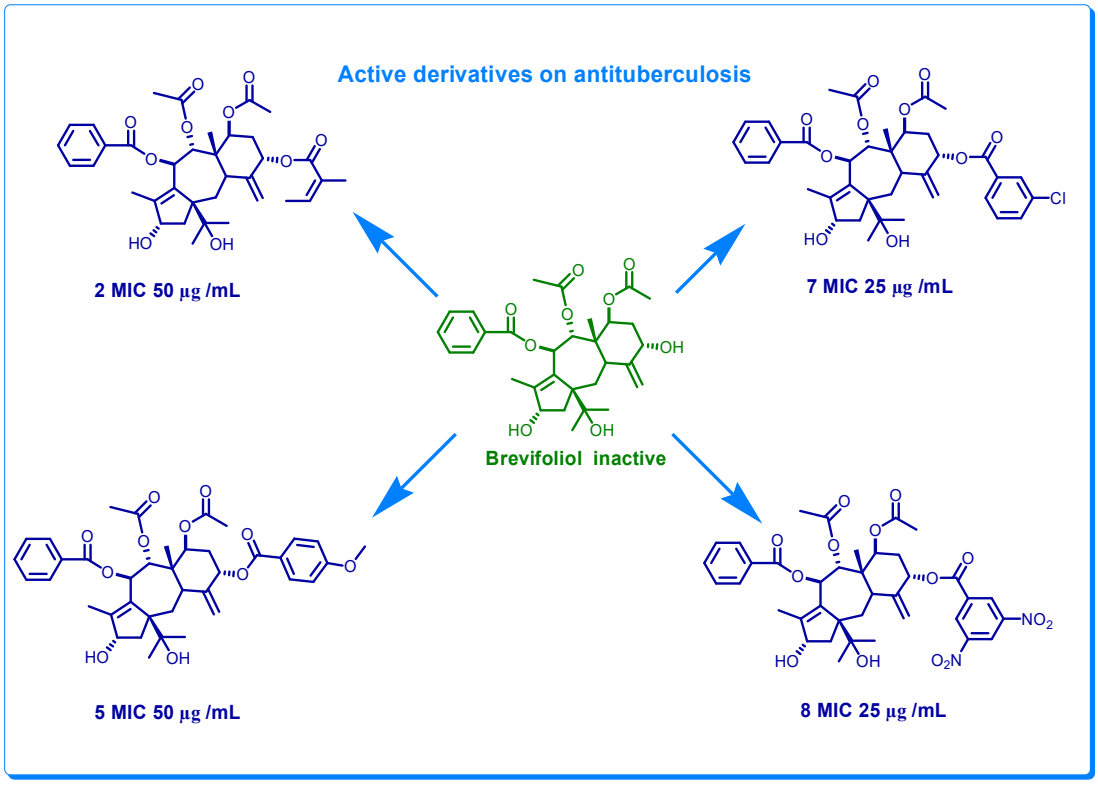
Abstract

The thesis accredit, **"Studies on synthesis of designed and isolated anticancer molecules"** involves designing of novel colchicine and estradiol based 2, 3-diarylnaphthofuran and 2, 3-diarylbenzofuran core, various prototypes, their synthesis and biological evaluation. Apart from these prototypes value addition of natural product of brevifoliol and total synthesis of biologically active natural molecule rugosa flavonoid-B have been undertaken. The studies mainly involve tubulin and caspase proteins as biological targets for anticancer agents. While, polyketide synthase-13 and enoyl-ACP reductase were biological targets for antitubercular agents.

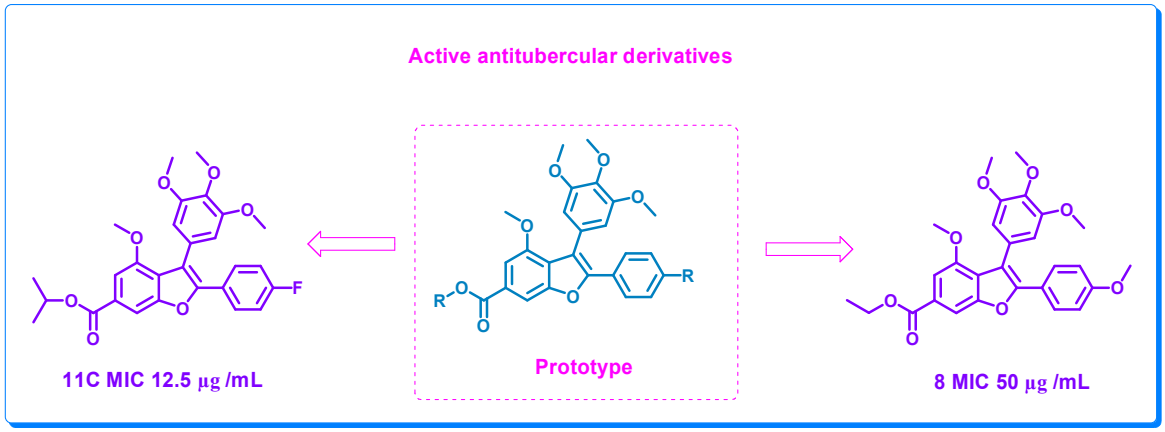
Brevifoliol, a secondary metabolite isolated from *Taxus wallichiana* needles has been derivatized as C5 esters using steglich esterification reaction. Eighteen diverse analogues were evaluated against a panel of human cancer cell lines like breast (MCF-7), colon (Colo-205), lung (A549) and prostate (PC-3) by MTT assay. Among these, two of the semi-synthetic analogues i.e. **11** and **14** (Chapter-2A) exhibited potent cytotoxicity selectively against PC-3, prostate cancer cell lines, at IC_{50} 3.89 µM and 5.02 µM respectively. In cell cycle analysis, analogue **11** induced S and G2/M phase arrest and induced apoptosis by activating caspase-3. Compound **11** showed moderate efficacy in *in-vivo* ehrlich ascites carcinoma in Swiss albino mice by reducing 55.85% tumour at 100 mg/kg i.p. dose. Further, compound **11** was well tolerated and found to be safe in Swiss albino mice up to 1000 mg/kg dose in acute oral toxicity. [B. Bhukya, et al, *Chem. Biol. Drug Design* **2020**; 95: 150-161]



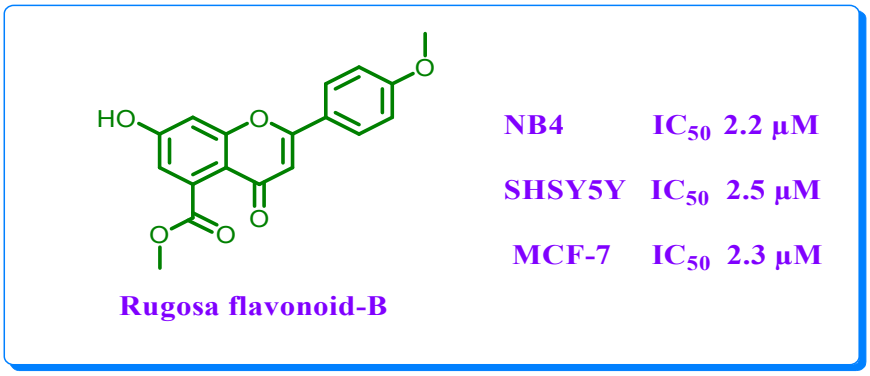
Further detailed literature search observed that many taxoids like taxol and 10-DAB derivatives were also active against the tuberculosis disease. Brevifoliol is a rearranged abeo-taxoid and its core structure is different than the taxoids class of compounds like taxol and 10-DAB. This is first report on antitubercular activity by brevifoliol. Its eighteen semi-synthetic ester derivatives of brevifoliol were screened for their anti-tubercular potential against *Mycobacterium tuberculosis* H37Rv avirulent strain. The 3-[chloro (**7**)] and 3, 5-[dinitro (**8**)] (Chapter-2B) benzoic acid ester derivatives were most active (MIC 25 µg/ml) against the pathogen. Further, *in silico* docking studies of the active derivative **7** with mycobacterium enzyme inhA (enoyl-ACP reductase) gave a LibDock score of 152.68 and binding energy of -208.62 Kcal/mol and formed three hydrogen bonds with SER94, MET98, and SER94. Similarly, when derivative **8** docked with inhA, it gave a LibDock score of 113.55 and binding energy of -175.46 Kcal/mol and formed a single hydrogen bond with GLN100 and Pi-interaction with PHE97. On the other hand the known standard drug isoniazid gave a LibDock score of 61.63, binding energy of -81.25 Kcal/mol and formed one hydrogen bond with ASP148. These molecular docking results and the way of binding pattern indicated that compound **7** and **8** bound well within the binding pocket of inhA and showed a higher binding affinity than the known drug isoniazid. Additionally, both the derivatives (**7** and **8**) showed no cytotoxicity towards the healthy liver cell lines CHANG. [B. Bhukya, et al, *Curr Topic Med Chem* 2020; 99:103784.]



Benzofuran is a biodynamic core, like anticancer, antitubercular, anti-inflammatory activity and many more. A total of seventeen 2, 3-diaryl benzofuran hybrids were designed, synthesized and screened for their anti-tubercular potential against *Mycobacterium tuberculosis* H37Rv avirulent strain. Out of seventeen, four derivatives showed significant activity against *M. tuberculosis* H37Rv a virulent strain (ATCC 25177) with MIC value ranging from 12.5-50 µg/mL but out of four, one derivative **11C** (Chapter-3A) was significantly active (MIC 12.5 µg/mL), which was further supported by the molecular docking score (-8.4) with respect to the first line anti-tubercular drug, isoniazid (-6.2) on the target polyketide synthase-13. All the derivatives were also evaluated for their cytotoxicity against the normal lung cell line L-132 by the MTT assay and no toxicity was observed up to 27.4 µg/mL concentration. This report on the antitubercular potential of benzofuran derivatives may be of great help in anti-tubercular drug development. [B. Bhukya, et al, *Bioorg Chem* 2020; 99:103784.]



Phytomolecules have great importance in our day to day life. We are taking natural products as medicine, supplements, aroma, in the pure form as well as in the form of herbal. Natural products and their derivatives effectively served as medicine last 50 years. Almost 61% of the FDA approved and pre-NDA candidates are natural product or their derivatives. By keeping the importance of natural products we have selected the rugosa flavonoid-B for the total synthesis. It is isolated from the common ornamental plant flower *Rosa rugosa* (Rosaceae) which is distributed in the temperate regions of eastern Asia and widely cultivated in Yunnam province. *Rosa rugosa* plant petals and buds are used in the food, incense in china. Its medicinal uses are against diarrhea, stomach ache and gynecological problems. Xue-Mei Gao group isolated rugosa flavonoid-B from this plant and reported its anticancer activity on three human cancer cell lines. We have selected it for total synthesis and its derivatization to generate more lead molecules to see its activity improvement. Its synthetic strategy has four steps and completed upto step-3 (Chapter-3B). Further final step and its derivatization are in progress in our lab.



Designed the pharmacophore by expecting that can exhibit dual nature drug like estradiol carrier type and tubulin binder in order to show the potent anticancer

activity. Breast cancer is most common invasive cancer which is second most leading cause of cancer deaths in women. We under took design and synthesis of diverse compounds on 2, 3-diaryl naphthofuran core. Out of sixteen new analogues four compounds exhibited significant antiproliferative activity against both hormone dependent (MCF-7) and hormone independent (MDA-MB-231) breast cancer cell lines. Among them the most active compound **7D** (Chapter-4) showed antitubulin effect. In molecular docking studies compound 7**D** occupied colchicine binding pocket with high affinity with crucial residual amino acids at β-tubulin. The compound **7D** found safe and non-toxic in Swiss albino mice up to 1000 mg/kg oral dose. The optimization of new lead compounds may yield some better candidates in future. [Manuscript submitted to *Bioorganic Chemistry*-2020]