THIAZOLIDINEDIONE (TZD) - AN INTERESTING SCAFFOLD IN ANTICANCER DRUG DEVELOPMENT

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Abstract - Thiazolidinediones (TZDs)viz., troglitazone, rosiglitazone and pioglitazone, were explored for their antidiabetic activity are now being unearthed for their anticancer activity. This is evident by the recent reports suggesting that these agents help in eradicating leukemic stem cells in combination with imatinib. However, these known TZDs cause several side effects and these have been attributed to their ability to activate peroxisome proliferative activated receptor γ (PPARγ) receptor. To evade the toxicity we synthesized various TZD containing moieties which would spare PPARγ. Synthesized molecules were screened on various malignant cell lines using SRB assay. Almost all moieties exhibitedexcellent GI_{50}values for activity on breast (MCF-7), oral (GURAV) and leukemia (K-562) cell lines in the range of 0.5μM- 80μM. Imatinib, a gold standard for chronic myeloid leukemia (CML)has started gaining resistance. Considering the recent reports on known TZDs in CMLpatients and resistance issue, we further continued our work with K562 cell line. Few molecules were found to arrest G0/G1 phase of cell cycle in dose(5 μM, 10 μM , 25 μM and 40 μM) and time dependent manner (at 10 μM and 20 μM). Two leads 3t and 3x were selected and further found to inhibit cyclin D1 and proliferating cell nuclear antigen (PCNA) at 10 μM and 20 μM using immunoblotting assay. The pharmacokinetic studies of these two derivatives were studied and reported. Moieties were further evaluated for in-vivo tumor regression activity alone and in combination with imatinib in nude mice. Molecules substantially reduced the tumor size in combination with imatinib. We would present an overview of our work on TZD's since almost a decade, in the course of which we have made several interesting observations.

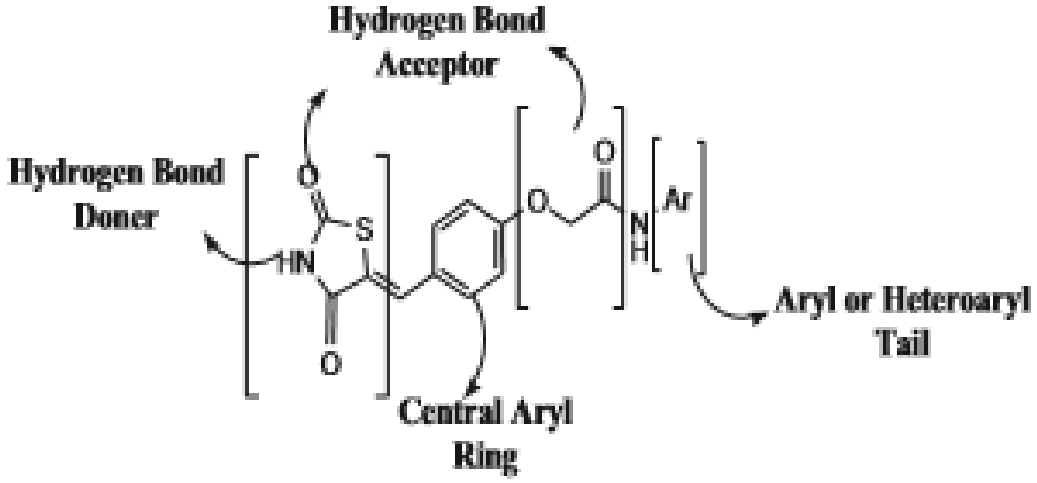


Figure 1: Schematic representation of the designed molecules.