CHAPTER 2

RESEARCH ENVISAGED AND PRESENT WORK
Review of literature in the preceding section reveals the contribution of antioxidative and signalling modulatory functionalities in discovery and development of drug candidates as promising therapeutic intervention in oxidative stress induced diseases. Structural description of anticancer agents and their SAR study indicates that certain functionalities including cinnamoyl (75), vanillyl (76), caffeoyl (77), syringyl (78), ferulyl (79) and many more can play a promising role in the drug development against cancer and other diseases.

Nature is known as rich sources of compounds with unique chemical features and pronounced biological activities, found in millions of species of plants, animals, marine, micro organisms. The natural products have played, and continue to play, a dominant role in the discovery of lead for the development of conventional drugs for the treatment of the human diseases. In addition to medicinally important plants, various weeds have also attracted the attention of many medicinal chemists for discovery and development of new drug candidates. One of such weed, which has attracted lot of interest of scientists in last three decade, is Lantana camara L. (Verbenaceae). It has encroached upon vast expanse of land area including pastures, orchards, tea gardens forests and agricultural lands in tropical and subtropical parts of the world and has imposed a great threat to grazing livestock and overall ecological balance. It is a rich source of a number of biologically active triterpenoids. Lantadene A 80 and lantadene B 81 are the major triterpenoids of the leaves of common pink-edged red flowering variety of weed Lantana camara L. (Verbenaceae). These compounds inhibited Epstein-Barr virus action in Raji cells induced by 12-O-tetradecanoylphorbol-13-acetate (TPA). LA 80 and LB 81 have also been reported to exhibit inhibitory effects on the two stage carcinogenesis of the mouse skin papiloma using 7,12-dimethylbenz[a]anthracene (DMBA) as inducer and TPA as promoter. These observations indicated that lantadenes have the potential to develop antitumor agents.
These compounds have structural difference in the side chain attached to C-22 position through ester linkage and this structural variation plays an important role in the activity.

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\begin{align*}
80 & \quad R = \text{COC(CH}_3)\text{=CHCH}_3 \\
\text{Lantadene A} \\
81 & \quad R = \text{COCH=CH(CH}_3)_2 \\
\text{Lantadene B} \\
82 & \quad R = \text{COCH(CH}_3)\text{CH}_2\text{CH}_3 \\
\text{Lantadene C} \\
83 & \quad R = \text{COCH(CH}_3)_2 \\
\text{Lantadene D}
\end{align*}
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Based on these observations, some of important functionalities were selected and proposed structure of lantadenes and hybrid compounds were submitted to DTP National Cancer Institute (NCI, Bethesda, USA). Selected lantadenes and hybrid compounds were synthesized and screened for in-vitro cytotoxic evaluation over a panel of 60 cell lines composite of nine different type of cancers including leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. NCI's COMPARE analysis was performed to find out probable anticancer molecular mechanism. As no molecular targets have been reported for these target vectors, which suggested that anticancer activity of test compounds were might be due to new molecular mechanistic targets. Furthermore, significance of lantadenes and integrated vanillyl and cinnamoyl functionalities was explored by selective cancer cytotoxicity and molecular mechanistic inhibitory potential on NF-κB and Akt. Probable molecular interaction with protein was determined by using automated molecular docking software Auto Dock 4.2. The compound 93 was evaluated for in-vitro cytotoxicity and apoptotic study including DNA fragmentation, Caspase-3 dependent induction of apoptosis and modulation of NF-κB, e-jun, Bax, Bel-2 and caspase-3 protein expression in B16F10 cells. The compound 93 was further evaluated for its in-vivo antitumor activity in B16F10 induced melanoma in C57BL/6 mice along with effects on liver enzyme and blood cells were also observed.