Apoptosis as a cellular target for cancer

Apoptosis is a physiological process that is important in tissue homeostasis. 63 Inadequate inhibition of apoptosis results in cell accumulation which is a hall mark of cancer, Excessive apoptosis leads to organ failure and neurodegenerative diseases such as Alzheimer and Parkinson diseases, AIDS, and ischemic diseases. Apoptosis can be initiated by many agents, including TNF-α and FAS ligand, as well as by chemotherapy and radiation.

Two major pathways involved in apoptosis are transmembrane death receptor (extrinsic) pathway and the mitochondrial (intrinsic) pathway. Activation of either pathway eventually leads to proteolytic cleavage and thus activation of caspases, that are responsible for many of the biochemical and morphological hallmarks of apoptotic cell death by cleaving a range of substrates in cytoplasm or nucleus. Out of many caspases, caspase 3 is the chief death effector protein, activation of which in turn is dependent on the activation of caspase 9. Disruption of mitochondrial function appears to be an early feature of apoptotic cell death. Several different biochemical changes have been shown, including the generation of reactive oxygen species (ROS), calcium flux, loss of the mitochondrial membrane potential, and cytochrome release. Apoptosis is also highly characterized by a series of typical morphological events, such as DNA fragmentation, chromatin condensation, membrane blebbing and cell shrinkage. Cells undergoing apoptosis ultimately dissemble into membrane enclosed vesicles (apoptotic bodies) that are engulfed by neighboring cells and phagocytes, thus preventing an inflammatory response (Figure 24).

Since a hallmark of human cancers is their resistance to apoptosis, there is a demand to develop novel strategies that restore the apoptotic machinery.

Numerous novel approaches like gene therapy, antisense strategies, recombinant biologics or combinatorial chemistry are employed in order to target specific apoptotic regulators. Therefore identification of new molecules that are able to modulate the apoptotic process, both as activators or inhibitors, with the ability to induce apoptosis in multidrug-resistant or apoptosis resistant tumor cell lines represents an attractive approach for the discovery and development of potential agents in cancer therapeutics.

Antimicrobial antibiotic

Bacterial infection continues to be a growing global health problem with the most widely accepted treatment restricted to antibiotics. However, the overuse, misuse of antibiotics and the emergence of resistance have triggered increased multidrug resistance to a number of antibiotics, affecting the therapeutic outcomes and leading to higher mortalities. Another important cause for the emerging resistance in various pathogenic strains towards available antibiotics is their ability to develop biofilms on living and nonliving surfaces, further increasing the difficulty in confronting bacteria because the extracellular matrix can act as a robust barrier to prevent the penetration of antibiotics and resist environmental stress.

Bacteria embedded in biofilm are found to be 1000 times more resistant to the antibiotics than their planktonic counterparts. 76, 77 Antibacterial resistance is currently implicated in 700, 000 deaths each year, and it is predicted that, the number of deaths per year will spiral to 10 million by 2050. 78 Many antibiotics available in the market such as pencillins (35), cephalosporins (36), tetracycline (37) (Figure 25) etc are now rendered

ineffective in treating the infections caused by multi drug resistant bacterial strains such as methicillin-resistant Staphylococcus aureus (MRSA).

As a result, the inability to completely eliminate bacteria and biofilms often leads to persistent infection. Therefore, it is of paramount importance to develop alternative antimicrobial agents while avoiding the generation of bacterial resistance. Objectives and aims of work Microtubules that are present in all eukaryotic cells due to their importance in mitosis and cell division are among the most successful targets for the development of new anticancer drugs. Many antimitotic drugs have been used with great success in the treatment of cancer. However due to certain limitations such as high neurotoxicity, drug resistance etc development of new tubulin targeting agents with less or negligible side effects are always desirable. The objective of the present work is to synthesize, new chemical libraries of several privileged heterocyclic scaffolds by employing lead modification strategy. These synthesized libraries are evaluated for their anticancer potential and are expected to serve as the source of new chemical entities for the development of newer and safer drugs.

During the past few decades it has been observed that the imidazobenzothiazoles /imidazopyridines and chalcone/quinoline derivatiaves displayed potential anticancer activity by inhibiting tubulin polymerization. The development of new hybrid conjugates that comprise of covalently linked two or more active pharmacophores in a single molecule with an intention to enhance the efficacy of hybrids by acting on multiple targets, displaying synergistic action and offer the possibility of overcoming drug resistance has emerged as an important concept in the cancer drug

discovery programme. Based on this view and considering their bioactivities a series of benzo[d]imidazo[2, 1-b]thiazole-chalcone conjugates and benzo[d]imidazo[2, 1-b]thiazole-quinolines were synthesized and evaluated in order to identify lead compounds and elucidate the mechanism of action behind the cytotoxic activity. Cell based assays such as cell cycle analysis, anti-microtubule and apoptosis were also studied (Chapter- II Section-A/Section-B).

In continuation of our research on microtubule targeting and apoptosis inducing anticancer agents we have also synthesized a series of 2-anilinopyridyl linked oxindole conjugates (Chapter III Section-A/Section-B). Considering the need of newer and safer chemotherapeutic drugs to combat microbial infections isatin-linked 2-hydrazinylbenzo[d]thiazole conjugates (Chapter IV) were synthesised following the same strategy of conjugating the two active scaffolds.