Chapter

1

# *Introduction*

# 1. INTRODUCTION

## 1.1. DRUG: FROM DISCOVERY TO DEVELOPMENT

Over the past 30 to 40 years there have been drastic changes in the way new medicines are developed. Before 1970s drug development was based on phenotypic assays and 'accidental findings', with an approval process that would often take two to three years to complete. But in recent years, medicinal chemistry has undergone a revolutionary change. Scientists now have a better understanding of the mechanisms leading to disease development. Thus, allowing the selection of 'targets' - regulators which are dysfunctional in the disease - allowing scientists to develop new drugs, which inhibit these cellular targets. As a result, the current research focuses on identifying suitable targets in the body and designing a drug to interact with that target. An understanding of the structure and the function of the target, as well as the mechanism by which it interacts with potential drugs is crucial to this approach.

Drug discovery, the process used to select a compound for drug development, is common in most pharmaceutical and biotechnology companies. The process begins with the identification of therapeutic targets and its validation, lead identification and its optimization, *in-vitro* studies, *in-vivo* studies, pharmacokinetics and safety studies in animals followed by phase I and phase II clinical trials in humans. It is a multidisciplinary approach including the disciplines of chemistry, and multiple branches of biology (from molecular to behavioural biology), biophysics, computer sciences, mathematics and engineering.

Drug design, an iterative process, begins with compounds that displays an interesting biological profile and ends with optimizing both the chemical synthesis and the activity profile of the molecule. Identifying structure activity relationships (SARs), identifying the pharmacophore, improving the target interactions and improving pharmacokinetic properties are the aspects involved in the drug designing. Drug design, also sometimes, referred to as rational design, and is applied in the discovery of novel lead drugs. Two types of drug design methodology are in vogue. They refer to ligand based drug design (or indirect drug design) and structure based drug design (or direct drug design). The former, relies on knowledge of other molecules that bind to the biological target of interest and the latter, depends on the knowledge of three dimensional structure of biological targets obtained through studies such as X-ray crystallography or NMR spectroscopy. Techniques such as SAR and QSAR are utilized for ligand based drug design. *In silico* techniques such as Molecular docking, Molecular dynamics simulation, Quantum chemical studies

and Homology modeling (if target structure is unavailable) are employed for designing of novel drugs in structure based methodology.

Modern drug discovery involves the identification of screening hits, optimization of those hits to increase the affinity, selectivity, efficacy/potency, metabolic stability, and oral bioavailability of drugs. Once a compound that fulfils all of these requirements has been identified, the process of drug development begins. Drug discovery can be mainly divided into four distinct steps *viz.* target identification and selection, target optimization, lead identification and lead optimization [Christoffersen *et al.,* 1995; Patrick, 2001]. Broadly, the overall steps described in Fig. 1.1.


**Fig. 1.1** Drug Development Process

## 1.2. MICROBIAL INFECTIONS AND ITS OVERVIEW

Antibiotics have always been considered as one of the wonder discoveries of the 20$^{th}$ century. The use of these "wonder drugs" have saved the lives and eased the suffering of millions of people. Antimicrobial resistance has cast a shadow over the medical miracles we take for granted, undermining every clinical and public health program designed to contain infectious diseases worldwide. The rapid evolution of antibiotic resistance poses a serious threat to the public health. Extremely resistant bacteria such as penicillin-resistant *Streptococcus Pneumoni,* methicillin-resistant *Stayphlococcus aureus* (MRSA) and

vancomycin resistant *Enterococci* account for a soaring percentage of hospital acquired infections [Marta *et al*., 2011]. Nowadays, the major concern is the emergence and spreads of microbes those are resistant to economical and effective first-line drugs. Therefore, there are surfeit of research going worldwide focused on the discovery of novel and potent antimicrobial agents, mainly arise by development of multidrug resistance among life threatening pathogens. However, in the past decade the significant advances in the technological fields of genomics, molecular & structural biology, high throughput screening and structural biochemistry have led to essentially new standards in the pursuit for novel antimicrobial agents [Learner and Beutel, 2002].

In the period between the 1930s and 1960s, a new class of antibiotic was introduced and majority of the drugs from this class are still employed in current clinical practice. Almost four decades have elapsed and only two new classes of antibiotics (oxazolidinone and lipopeptides) entered into the market which is efficient against Methicillin and/or Vancomycin-resistant Gram-positive bacteria in year 2000 and 2003. Although several antibiotics were discovered more than 50 years ago, their mode of action is still not precisely known. However, majority of antimicrobials are directed at a small group of well-validated targets, suggesting that these are the most effective ways to kill cells. So, there is a requirement to develop new replacement drugs immediately which is effective against resistant bacteria, having lesser toxicity as well as economical also. Another approach is to develop such agents that must target essential bacterial pathways, which may have new modes of action or even interfere with novel bacterial targets. Many essential bacterial proteins have been identified as potential drug targets. However, an ideal target is recognized as that different from existing targets, essential for microbial cell survival, highly conserved in a clinically relevant spectrum of species, absent or radically different in man, easy to assay, and has an known biochemistry. As a result, research into these targets, either in the development of novel inhibitors or modification of existing agents, is very important for future drug development.

**Molecular basis for cell selectivity**

Despite the structural diversity, the ionisable property of heterocyclic drugs allows it to favourably interact with membranes, which are composed of amphipathic lipids (Fig. 1.2). Many drugs are considered to exert toxicity by permeabilizing the lipid matrix of cell membranes, although intracellular targets have also been suggested for certain cases. The cationic property of ionisable heterocyclic drugs mainly contributes to cell selectivity,

because the surface of bacterial membranes is more negatively charged than that of mammalian cells (Fig. 1.2). The cell membranes of bacteria are rich in acidic phospholipids, such as phosphatidylglycerol and cardiolipin. As an extreme case, phosphatidylglycerol composes <90% of the phospholipids in the inner membrane of *Staphylococcus epidermidis* [Komaratat and Kates, 1975]. The cell walls also contain anionic molecules, such as lipopolysaccharides in the outer membrane of Gram-negative bacteria and teichoic acids and lipoteichoic acids in the peptidoglycan of Gram-positive bacteria.

In contrast, acidic phospholipids are usually sequestered in the inner leaflets of plasma membranes in the case of mammalian cells [Verkleij *et al*., 1973] (Fig. 1.2). The outer leaflets are mainly composed of Zwitterionic phosphatidylcholine and sphingomyelin, although negatively charged gangliosides are present as minor species. Hydrophobic interaction between the hydrophobic face of an amphipathic drugs and zwitterionic phospholipids on the cell surface play a major role in the interaction of these with mammalian cell membranes.

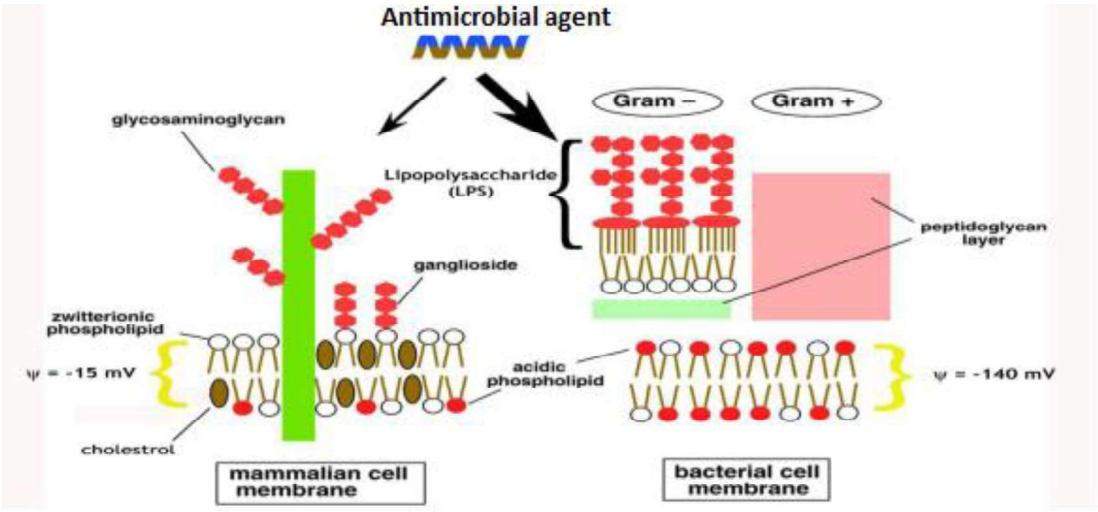


**Fig. 1.2** Differences between composition of mammalian and bacterial cell membranes. Mammalian membrane is composed primarily of zwitterionic lipids and sterols whereas bacterial membrane is made up of negatively charged lipids. Gram negative bacteria differ from Gram positive bacteria; Gram negative bacteria possess thinner peptidoglycan layer than Gram positive bacteria and an additional outer layer containing lipopolysaccharide. Electrostatic interaction between positive charged heterocycles and negatively charged component (red) of bacteria is the major driving force for their initial interactions [figure modified from Sims *et al*., 1974].

One important qualitative difference between the microbial and mammalian cells is the presence of a cell wall in the former. In consequence, enzymatic pathways leading to the formation of the cell wall are potential targets for antimicrobial drugs. One such target enzyme, i.e. L-glutamine: D-fructose-6-phosphate amidotransferase, known under the trivial name of glucosamine-6-phosphate synthase, is important for antimicrobials [Milewski *et al*., 1988]. Glucosamine-6-phosphate (GlcN-6-P) synthase is a ubiquitous enzyme and its activity has been detected in a number of organisms and tissues. Obviously, glucosamine-6-phosphate, the product of this enzyme, is indispensable for fungi as well as for bacterial cells. The product GlcN-6-P is a precursor of uridine diphospho-*N*-acetyl glucosamine from which other amino sugar-containing molecules are derived. One of these products, *N*-acetyl glucosamine, is an important constituent of the peptidoglycan layer of bacterial cell wall and fungal cell wall chitin. It has shown that even a short-time inactivation of GlcN-6-P synthase in fungal cells is lethal for the pathogen [Milewski 2002].

Most alarming of all are diseases where resistance is developing for all currently available drugs; current trends suggest that some diseases will have no effective therapies within the next ten years. So, there is a requirement to develop new replacement drug immediately which is effective against resistant bacteria having lesser toxicity as well as economical also.

## 1.3. CANCER AND ITS OVERVIEW

Cancer, derived from the Greek word “Karkinos” (meaning-crab), is the rapid creation of abnormal cells that can grow beyond their boundaries, invade adjoining parts of the body, and spread to other organs. Neither the etiology nor the way by which it causes death is understood in most cases. Cancer is a notable complex, widespread and lethal disease characterized by uncontrolled growth and spread of abnormal cells, in which cells can be aggressive (grow and divide without respect to normal limits), invasive (invade and destroy adjacent tissues) and/or metastatic (spread to other locations in body). These malignant properties of cancer differentiate them from benign tumors, which do not invade or metastasize and are self-limited in their growth. Cancer is caused by both external factors (tobacco, infectious organisms, chemicals, and radiation) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). It may affect people at all ages, even foetuses, but the risk factor for its common varieties tends to increase with age and weight [Kushi *et al.,* 2012]. Cancer can

be treated by chemotherapy, radiation-therapy, surgery, immunotherapy, monoclonal antibody- therapy and other methods. The choice of therapy depends upon the location, grade of the tumor and the stage of the disease, as well as the general state of the patient. The design and development of novel antitumor drugs that could effectively inhibit proliferative pathways are needed urgently.

Cancer is an enormous global health burden, touching every region and socioeconomic level. Today, cancer accounts for one in every eight deaths worldwide – more than those due to combined HIV/AIDS, tuberculosis, and malaria. Cancer chemotherapy targeting tumor progression represents one of the most relevant challenges to the chemists and oncologists. According to global cancer statistics released by the American Cancer Society, the total number of deaths due to cancer in 2014 was 14.6 million, or about 40,000 deaths each day, with 38% and 62% in developed and developing countries. Moreover, the global cancer burden is growing at an alarming pace. It is projected that by 2050, 27 million new cancer cases will be registered and 17.5 million deaths may occur in the world, simply due to the growth and aging of the population.

Ovarian and Cervical cancer are the most common type of cancers in womens and is a major cause of morbidity and mortality in women worldwide. Ovarian cancer is the fifth most common cancer in women in the UK with around 6800 new cases each year. Survival rates have increased since the 1970s, with the latest figures showing 5-year survival at 40%. Human papillomavirus (HPV) represents a group of widely diversified viruses, the etiological agent, is detectable in nearly all types of cervical cancers. High-risk HPVs (types 16 and 18) are associated with the malignant lesions of the genital regions of majority of the cervical carcinomas. HPV 16, the most prevalent of the high-risk type HPVs, is responsible for approximately 54% and HPV 18 for 18% of cervical cancer [Jenkins *et al*., 2008]. Together, HPV16 and 18 are the cause of 70% of cervical cancers worldwide. Overall, it is estimated that 5.2% of all cancers are attributable to HPV. Two prophylactic HPV vaccines i.e., Gardasil and Cervarix are commercially available since 2006 [Ghittoni *et al.,* 2015]. Modern advances in cellular and molecular biology have enhanced our understanding of the various mechanisms of cancer. So, medicinal chemists are currently focusing on novel biological targets with the aim of providing new specific and potent chemotherapeutic agents that selectively destroy cancer cells while sparing their healthy counterparts.

Apoptosis, a physiological mode of cell death, serves as a defense mechanism in higher eukaryotes and plays crucial role in the prevention of tumor cell proliferation [Thompson *et al.,* 1995]. Its deregulation is largely believed to be involved in the pathogenesis of

cancer, and there are many antitumor compounds that induce the apoptotic process in tumor cells [Cummings *et al.,* 2004]. Cytotoxicity and genotoxicity of anticancer drugs to the normal cells are major problems in cancer therapy and endanger the risk of inducing secondary malignancy [Aydemir and Bilaloglu, 2003]. Thus, the development of drugs, possessing least cytotoxicity capable to effectively trigger apoptosis in tumor cells, has been receiving considerable attention. This therapeutic approach has aroused lot of interest amongst researchers and a great deal of efforts has now been focused on the design and development of variety of anticancer drugs.

In 1996, analysis of anticancer drugs approved by the FDA revealed that two-thirds of the anticancer drugs currently used by oncologists for cancer treatment were NCI-sponsored Investigational New Drugs. Different classes of anticancer drugs are listed in Table 1.1

**Table 1.1** Classification of chemotherapeutic agents with representative drugs

| **CHEMOTHERAPEUTIC AGENTS** | |
|---|---|
| **DNA CROSS LINKING AGENTS**<br><br>**(Alkylators & Organometallics)** | **Nitrogen mustard & Aziridine mediated alkylators:** Cyclophosphamide, Ifosfamide, Chlorambucil, Melphalan, Mechlorethamine hydrochloride |
| | **Nitrosoureas:** Carmustine, Lomustine, Streptozotocin |
| | **Alkyl sulfonate:** Busulfan |
| | **Ethyleneimines:** Triethylene thiophosphoramide |
| | **Procarbazine & Triazines:** Procarbazine hydochloride, Dacarbazine and Temozolamide |
| | **Platinum compounds:** Cisplatin, Carboplatin, Oxaliplatin, Satraplatin |
| **ANTIMETABOLITES** | **Folate antagonist (Indirect inhibitors of thymidylate synthase):** Methotrexate, Pemetrexed |
| | **Purine antagonist (Amidophosphoribosyl Transferase inhibitors):** Thioguanine, Mercaptopurine |
| | **Pyrimidine antagonist (dTMP synthesis inhibitors):** 5-Fluorouracil, Floxuridine, Capecitabine |
| | **Deoxyribonucleotide antagonist:** Hydroxycarbamide |
| | **DNA polymerase inhibitors:** Cytarabine, Gemcitabine, Fludarabine, Cladribine and Clofarabine |

| | |
|---|---|
| **TOPOISOMERASE INHIBITORS** | **Topoisomerase-I inhibitors:** Irinotecan, Topotecan, Camptothecin |
| | **Topoisomerase-II inhibitors:** Etoposide, Teniposide, Doxorubicin, Daunorubicin, Mitoxantrone |
| | **Topoisomerase I and II inhibitor:** Saintopin |
| **MITOSIS INHIBITORS**<br><br>**(Spindle poison/ cytoskeletal disruptors)** | **Taxanes:** Paclitaxel, Docetaxel |
| | **Vinca alkaloids:** Vinblastine, Vincristine and Vindesine |
| | **Epothilones:** Epothilone B |
| **HISTONE DEACETYLASE INHIBITOR** | **Hydroxamic acid derivative:** Vorinostat (Suberoylanilide hydroxamic acid, SAHA) |
| | **Depsipeptide derivatives:** Romidepsin |
| **KINASE INHIBITORS** | **Proteasome inhibitors:** Bortezomib, Carfilzomib |
| | **Tyrosine kinase inhibitor:** Erlotinib, Gefitinib, Imatinib |
| | **Vascular endothelial growth factor A (VEGF-A) inhibitor:** Bevacizumab, Axitinib |
| | **Serine/threonine kinase Inhibitors:** GSK2110183 |
| **DNA INTERCALATING AGENTS** | **Glycopeptide antibiotics:** Bleomycin $A_2$ and $B_2$ |
| | **Polypeptide antibiotics:** Actinomycin D |
| | **Azirinopyrrolo-indole-4,7-dione derivative:** Mitomycin C |
| **PHOTOSENSITIZERS** | **Pentanoic acid derivative:** Aminolevulinic acid<br><br>**Propanoic acid derivative:** Efaproxiral |
| **TUMOR SUPPRESSOR GENE ACTIVATORS** | **Retinoids:** Tretinoin, Isotretinoin, Alitretinoin, Bexarotene |
| **DNA DEMETHYLATORS** | Azacitidine, Decitabine |
| **ANTIBIOTICS** | Bleomycin, Dactinomycin, Mitomycin, Doxorubicin, Daunorubicin, Carminomycin, Rubidazone |
| **MISCELLANEOUS** | Hydroxyurea, L-Asparaginase |

## 1.4. BENZOTHIAZOLE RING AND ITS BIOLOGICAL ACTIVITIES

Benzothiazole, a heterocyclic compound constitutes an important scaffold of drugs, which can serve as unique and versatile ligand for experimental drug design and have attracted attention because of their varied biological activities. The activities pertaining to benzothiazole ring includes antitumor [Shi *et al*., 1996], antimicrobial [Catalano *et al*., 2013], schistosomicidal [Mahran *et al*., 2007], anti-inflammatory [Gupta *et al*., 2010], anticonvulsants [Siddiqui *et al*., 2007], antidiabetic [Navarrete-Vazquez *et al*., 2009], antipsychotic [Arora *et al*., 2010], neuroprotective [Anzini *et al*., 2010] and diuretic [Yar and Ansari, 2009] (Fig. 1.3).

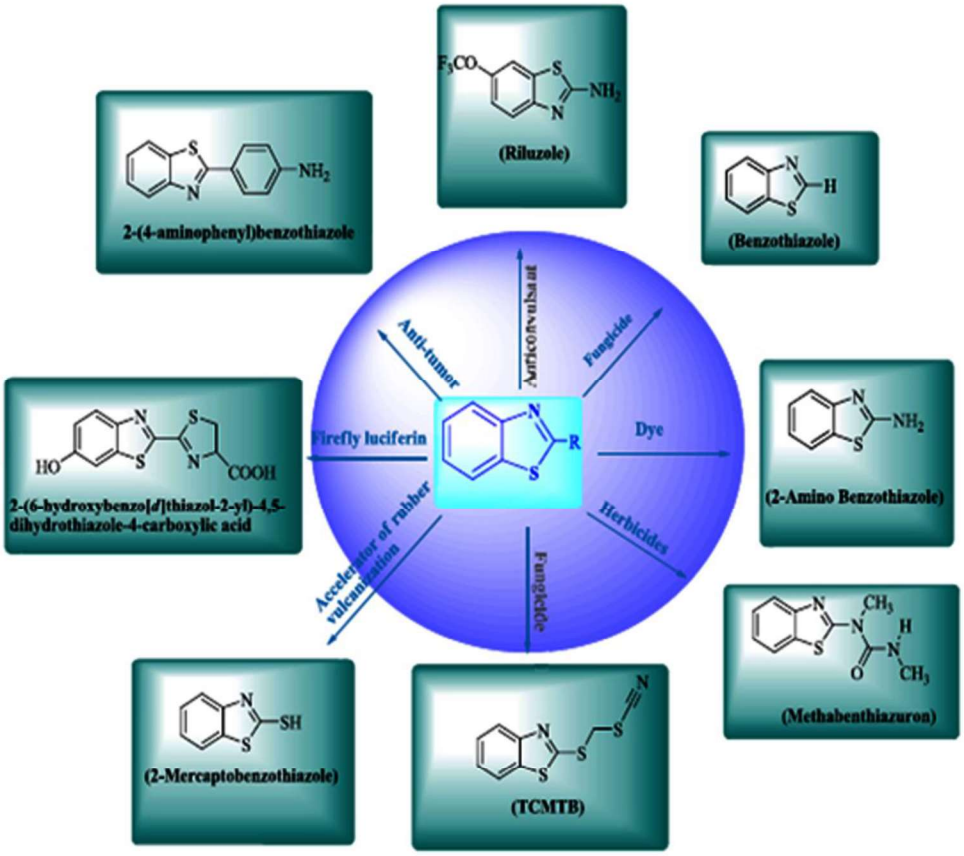


**Fig. 1.3** Benzothiazole, a multifunctional nucleus

Many of the bioactive molecules contain 2-(4-aminophenyl) benzothiazole moiety such as antitumor (1, 2), orexin receptor antagonist (3) [Bergman *et al*., 2006] and the Gram-positive selective antibacterial (4) [Ali *et al*., 2001] (Fig. 1.4). Structure-activity relationship (SAR) carried out on these heterocycles have shown that positions 2 and 6 are crucial for antibacterial activity against Gram-positive and Gram-negative bacterial strains [Yildiz-Oren *et al*., 2004]. Some of the bis-benzothiazole derivatives exhibit their

importance in amyloid-imaging [Wu *et al.* 2007], as vulcanization accelerators and also as starting materials for the synthesis of various drugs. In addition, the benzothiazole ring is present in various marine or terrestrial natural compounds (5-11), which have useful biological activities (Fig. 1.5). Due to their importance in pharmaceutical utilities, the synthesis of various benzothiazole derivatives is of considerable interests.

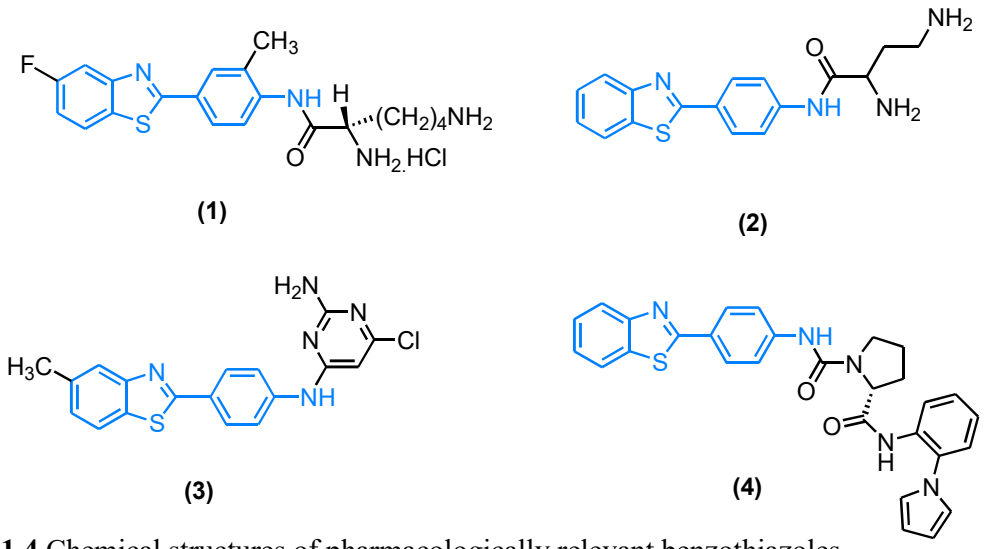


**Fig. 1.4** Chemical structures of pharmacologically relevant benzothiazoles

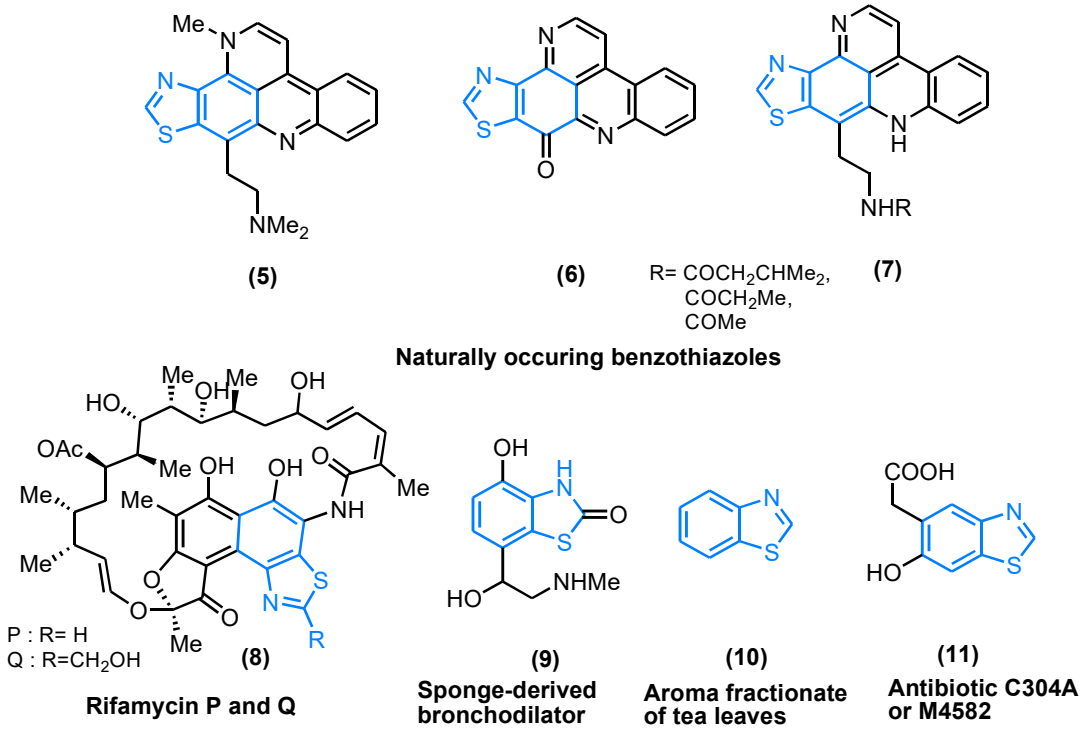


**Fig. 1.5** Chemical structures of biologically important benzothiazole compounds

Several successful clinical drugs such as ethoxzolomide (12), frentizole (13), riluzole (14), zopolrestat (15) and so on and the well-known amyloid imaging agent thioflavin T (16) contain benzothiazole nucleus (Fig. 1.6). These drugs have applications in the treatment of various diseases/disorders, which are outcome of impaired physiological processes in humans. Ethoxzolomide, the sulfonamide drug with a core benzothiazole ring serves as diuretic and frentizole, the urea derivative of benzothiazole is used as antiviral as well as immunosuppressive agent. On the other hand, riluzole is a glutamate receptor antagonist, which is used to treat amyotrophic lateral sclerosis. In addition, it is also known to possess antidepressant activity and have clinical significance in the treatment of anxiety disorders. Zopolrestat is another important drug containing benzothiazole core with antidiabetic effects.

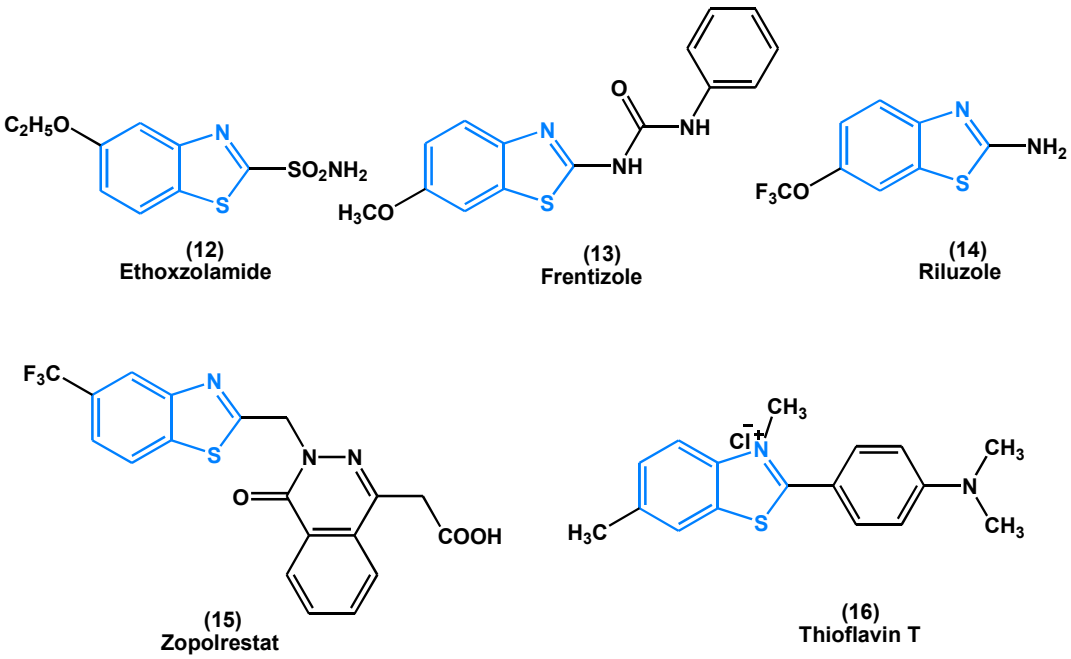


**Fig. 1.6** Drugs containing benzothiazole nucleus

During 50s of the twentieth century, a large number of 2-aminobenzothiazoles were extensively studied and formed part of one of the privileged structures in medicinal chemistry [Piscitelli *et al.,* 2010 and Reddy *et al.,* 2007]. It was reported to have cytotoxic effect on cancer cells which are comparable to that of cisplatin [Hutchinson *et al.* 2003]. Some of the important benzothiazole derivatives with anticancer properties are shown in Fig. 1.7. Among these, frentizole (17) is a nontoxic antiviral and immunosuppressive agent used clinically in rheumatoid arthritis and systemic lupus erythematosus. Similarly,

substituted benzothiazoles such as 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610) (18) have been shown to exhibit exquisite potential ($GI_{50}$ <0.1 nM) and selective *in-vitro* antitumor properties in human cancer cell lines (e.g., colon, nonsmall-cell lung and breast subpanels of the National Cancer Institute (NCI) 60 human cancer cell line screen). Other benzothiazoles such as 2-(4-amino-3-methylphenyl) benzothiazole (DF 203) (19) and the 2-(4-amino-3-methylphenyl)-5-fluoro benzothiazole (5F 203) (20) were found to activate the Arylhydrocarbon Receptor (AhR) via translocation from the cytosol to the nucleus. The induced cytochrome P450 CYP1A1 enzyme activity was determined in these, that subsequently led to the generation of a reactive chemical intermediate responsible for the generation of DNA adducts only in sensitive tumor types (e.g., mammary and ovarian tumor cell lines) [Kumbhare *et al.,* 2012].

Another compound, a benzothiazole-substituted 4-hydroxy cyclohexadieneone (AW 464) (21), is the prototype of a new series of "quinols" with potent antitumor activity against renal and colon cancer cell lines that affects cell-signaling events downstream of the redox regulatory protein thioredoxin [Bradshaw *et al.,* 2005 and Mukherjee *et al.,* 2005]. Compound (22), $^{11}$C-methylated derivative of benzothiazole developed as an amyloid-affinic agent, is in clinical trials for early diagnosis of Alzheimer's disease. The metabolic instability limited its clinical application and thus potential use of metabolically stabilized (fluorinated) benzothiazoles (23) in the Alzheimer's diagnosis has been reported [Henriksen *et al.,* 2007]. A related structure, 2-(4-Aminophenyl)benzothiazole (24) and its corresponding N-acetylated derivatives (25) showed surprisingly remarkable anticancer activity against certain cancer cell lines particularly against breast, colon and ovarian in *in-vitro* anticancer screening program of the NCI [Chua *et al,.* 1999 and Kashiyama *et al.,* 1999]. A prodrug, phortress compound (26) exhibited potent antitumor activity against human mammary tumor xenografts and is currently in phase II clinical trial in UK.

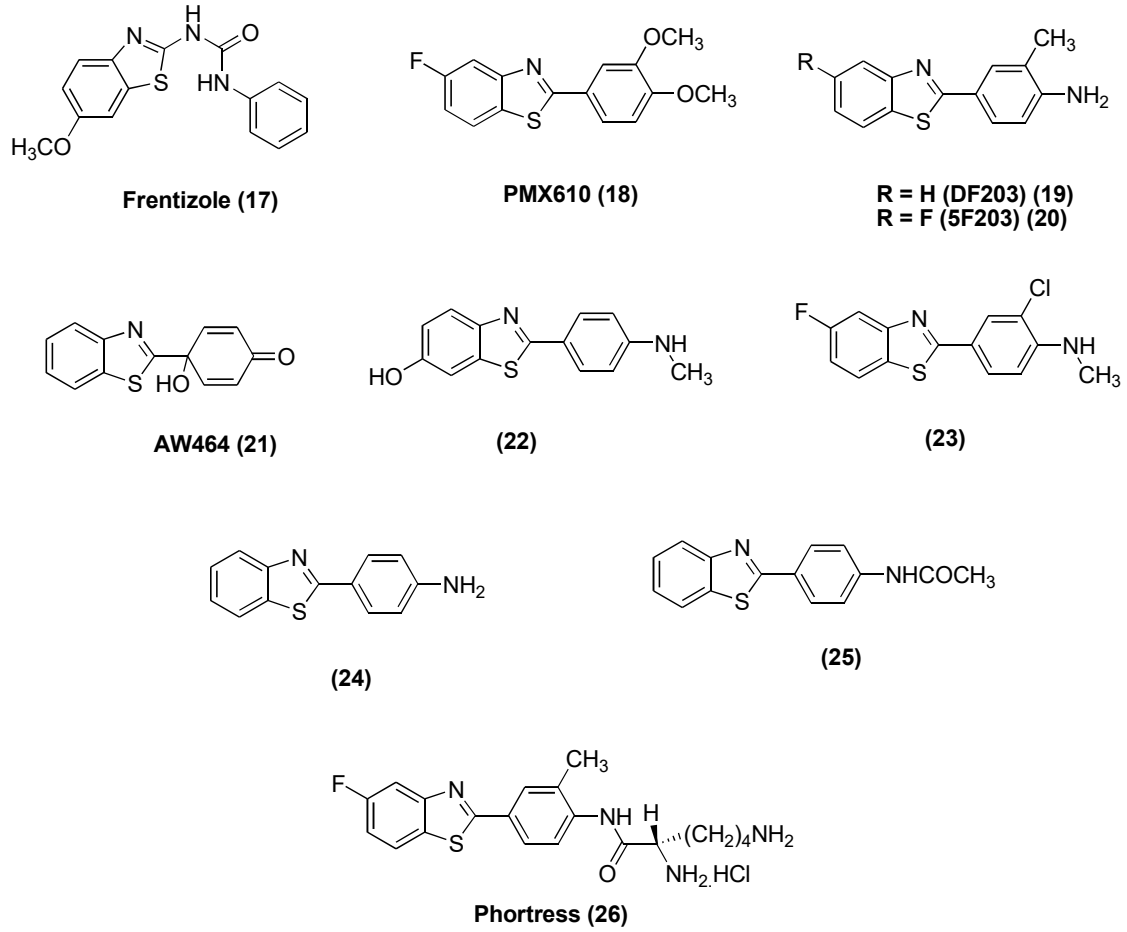


**Fig. 1.7** Chemical structures of benzothiazole derivatives with anticancer properties.

Many effective antimicrobial agents contain a heterocyclic moiety within their structure; in particular, substituted benzimidazole, benzoxazole and benzothiazole derivatives received special attention as they belong to a class of compounds with proven utility in medicinal chemistry [Daidone *et al*., 1990]. They possess different biological properties such as chemotherapeutical, antibacterial, antifungal, and antiviral activities, with low toxicity for the antimicrobial therapeutic use in man [Haugwitz *et al.,* 1982 and Hisano *et al.,* 1982]. Structure–activity relationship (SAR) studies carried out on these types of heterocycles have shown that positions 2 and 6 are crucial for antibacterial activity against Gram-positive and Gram-negative bacteria strains [Yildiz-Oren *et al*., 2004]. Many of the investigations indicated that the presence of hydrogen bonding domain e.g., amide (–CONH–) seems to be valuable in the structures of antimicrobials [Jagessar and Rampersaud, 2007]. Patel and his co-workers identifed an agent (compound 29, Fig. 1.8), comprises of benzothiazole – acetamide system which plays an essential role in promising antimicrobial activities [Patel *et al.,* 2012].

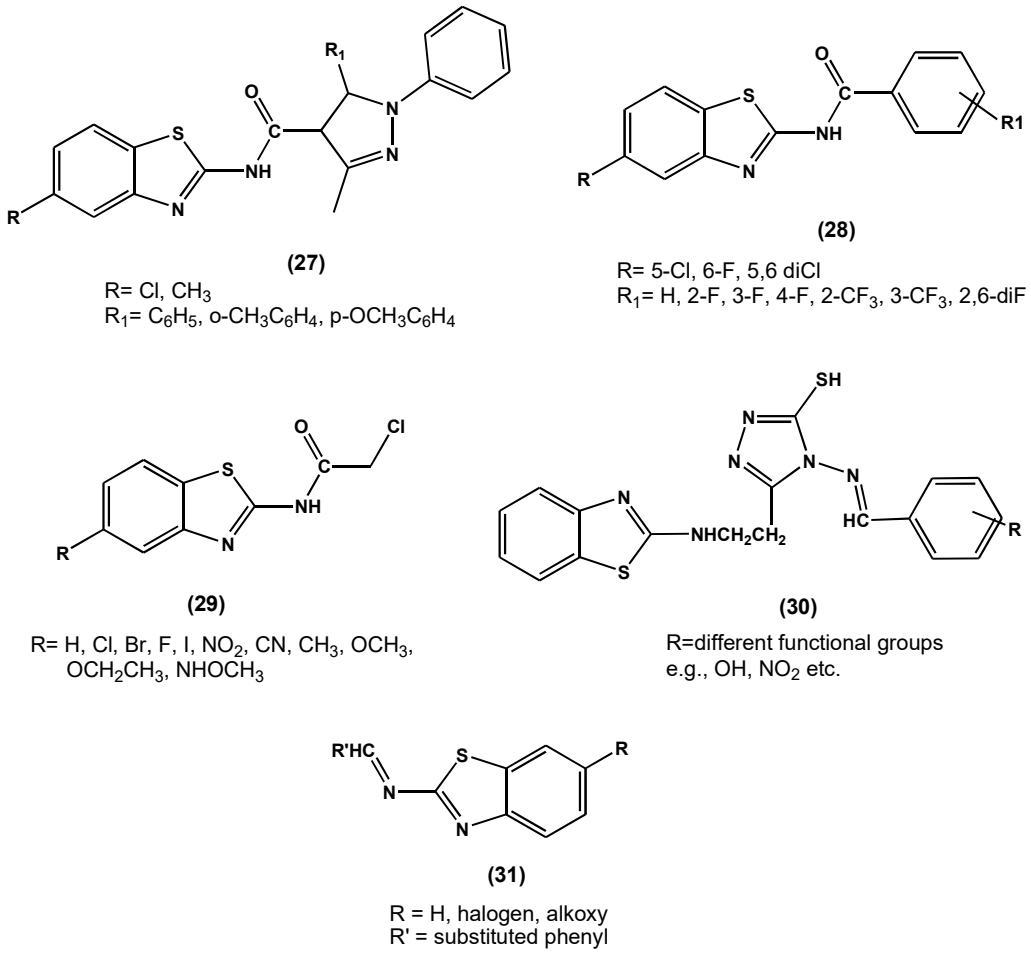


**Fig. 1.8** Chemical structures of benzothiazole derivatives with antimicrobial properties.

## 1.5. TARGETS FOR ANTIMICROBIAL AND ANTICANCER DRUGS

The most innovative approach to microbial therapy is the identification of new targets and subsequent discovery of compounds that act on these targets. There are approximately 200 conserved essential proteins in bacteria, but the number of currently exploited targets is very small. The most successful antibiotics hit only three targets or pathways: the ribosome (which consists of 50S and 30S subunits), cell wall synthesis and DNA gyrase or DNA topoisomerase (Fig. 1.9). Progress towards the characterization of the biology has been stimulated by the development of technology to disrupt bacterial cell wall and its membrane.

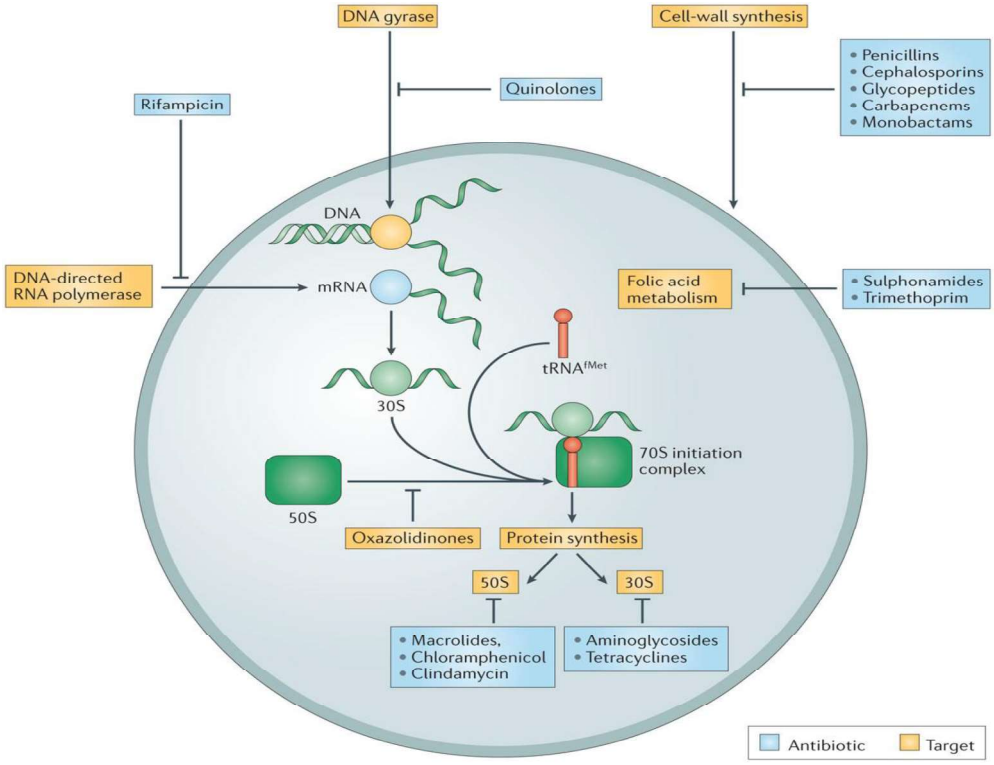


**Fig. 1.9** Multiple targets of antibiotics [Lewis, 2013]

Benzothiazole ring belongs to the privileged scaffolds in modern medicinal chemistry particularly in discovering new anticancer agents. It modulates growth of tumour cells through regulation of multiple cell signalling pathways including cell proliferation, cell survival, caspase activation and protein kinase pathway. These were proposed as inhibitors of fatty acid amide hydrolase (FAAH) [Wang *et al.,* 2009], Raf kinase (Raf-1) [Song *et al.,* 2008] and B-cell lymphoma protein BCL-2 [Zheng *et al.,* 2007]. Many benzothiazole derivatives exhibited their antitumor activity through different mechanisms including, protein tyrosine phosphatase-1b [Sparks *et al.,* 2007] topoisomerase II [Choi *et al.,* 2006], and lysophosphatidic acid acyltransferase-b (LPAAT-b) [Gong *et al.,* 2004], and as ROCK-II inhibitors [Yina *et al.,* 2009]. In the closely related area, protein kinases have emerged as one of the most important targets for drug discovery. Besides growth factor receptor tyrosine kinases, numerous other protein kinases implicated in malignancies have been identified including non-receptor kinases such as Bcl-Abl and Src kinases. In addition, the cell cycle regulators (cyclin-dependent kinases, p21 gene) and apoptosis modulators (Bcl-2 oncoprotein, p53 tumor suppressor gene, survivin protein, etc.) have also attracted renewed interest as potential targets for anticancer drug discovery.

New cancer targeted therapies that make use therapeutic antibodies or small molecules have made treatment more tumor specific and less toxic. Nevertheless, there remain several challenges for the treatment of cancer, including drug resistance, cancer stem cells, and high tumor interstitial fluid pressure. Targeted therapy refers to a new generation of cancer drugs designed to interfere with a specific target protein that is believed to have a critical role in tumor growth or progression. This approach contrasts with the conventional cytotoxic chemotherapeutics that have been used in major cancer therapy in past decades. The molecular identification of cancer antigens has opened new possibilities for the development of effective immunotherapies, antibodies therapy and ligand-targeted therapy for cancer patients (Fig. 1.10).

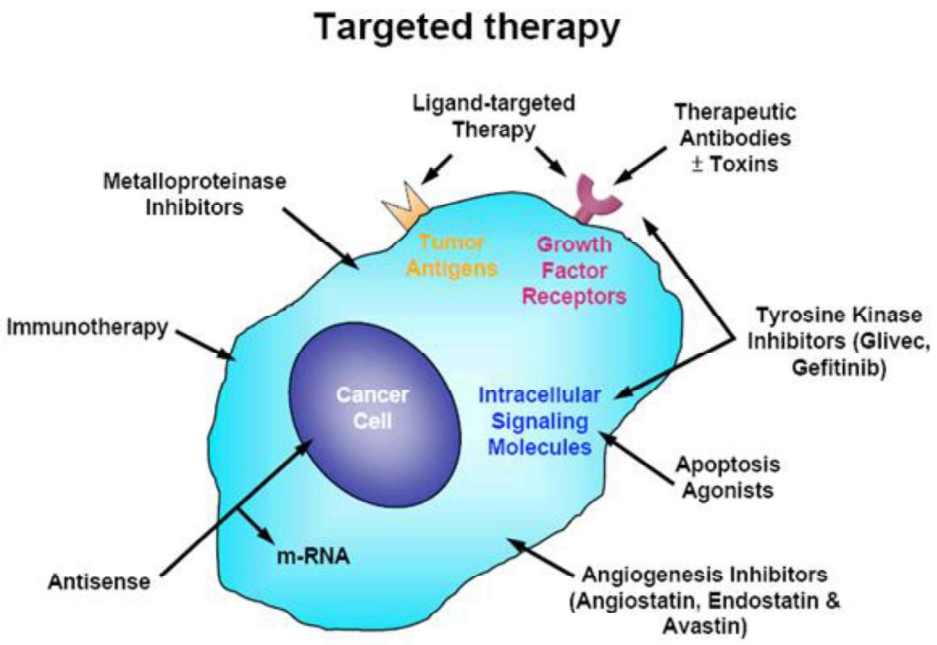


**Fig. 1.10** Targeted therapy for anticancer agents

Although, major advances have been made by medicinal chemists in the chemotherapeutic management but the clinical needs are still largely not met due to development of resistance to antimicrobial and anticancer drugs and resulting in inevitable morbidity and mortality. Thus, urgent measures are needed now to reduce the current and future burden of disease.