AN OVERVIEW OF IMIDES AND THEIR ANALOGUES AS ANTICANCER AGENTS

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ABSTRACT

In this review article, we highlight the history of cancer immunotherapy; different types of cancer diseases, different stage of cancers, gene mutations are involved in cancer pathogenesis as well as additional information has been obtained that can be useful for early diagnosis and proper treatment. We also highlight the current pitfalls and limitations of cancer checkpoint immunotherapy and how novel research in the fields of personalized cancer vaccines, autoimmunity, the microbiome, the tumour microenvironment, and metabolomics is aiming to solve those challenges. This review also gives an overview of the many discoveries and the progression of the use of some thalidomide analogues especially naphthalimides as anticancer agents and their applications to date; focusing mainly on mono-, bis-naphthalimide based structures, and their various derivatives (e.g. amines, amino acids, heterocyclic systems).

Keywords: anti-cancer; imides; thalidomide; naphthalimides; synthesis, cytotoxicity.

Introduction

1.1 What is cancer?

The word “Cancer” was credited by a Greek physician Hippocrates (460 - 370 BC), who is furthermore considered the "Father o f Medicine." Hippocrates used the terms “carcino” and “carcinoma” to describe non-ulcer forming and ulcer-forming tumors. Carcinoma (cancer arising from epithelial cells) is the most common type o f cancer (Nema et al., 2013). Nowadays, cancer is defined a group of diseases characterized by uncontrolled cell division and uncontrolled cell growth. The resulting mass, or tumor, can invade other tissues, either by direct growth into adjacent tissue (invasion) or by migration of cells to distant sites (metastasis).Another Roman physician Galen (130-200 AD), used the word oncos’ (Greek for swelling) to describe tumors. A mature human comprises about 1015 cells; scores of them divide and differentiate in order to renew organs and tissues, which require cell turnover (Bertram, 2001). However, if the cells do not stop dividing, they may show the way to cancer. Characteristically, cancer is an uncontrolled proliferation of cells which become structurally abnormal and possess the ability to detach them from a tumor and begin a new lump at a remote site within the host (National Cancer Institute, 2009).

The goal of an ultimate conquest of cancer remains a distant hope. Cancer cells closely resemble normal cells, as cancer results from uncontrolled growth of otherwise normal cells (Cooper, 1992 chapter 1). Most of the drugs currently available for use in cancer treatment act against all rapidly proliferating cells. Thus, they kill not only cancer cells but also some normal cells, particularly those that are rapidly dividing. The effectiveness of treatment is often severely limited by the toxic side effects of the drugs. The fundamental problem in cancer treatment is to kill cancer cells selectively without adverse side effects to the patient (Cooper, 1992 chapter 1).

1.2. Causes of Cancer:

Tobacco smoking is undoubtedly the major cause of human cancer; other common causes of human cancer include alcohol abuse, radiation, carcinogenic medicines, and occupational carcinogens, each of which accounts for only a few percent of total cancer deaths (Cooper, 1992 chapter 7). Taken together, it is estimated that up to 80% of human cancers may be attributable to environmental risk factors. Most cancers are a result of a mutation in the sequence of DNA (Cooper, 1992 chapter 3).

2. Classification of cancer:

Cancer can occur anywhere in the body. Broadly, cancers were classified as either solid (for example breast, lung or prostate cancers) or liquid (blood cancers). Cancer was further classified according to the tissue in which it arises:

2.1. Carcinoma

Carcinomas are cancers that occur in epithelial tissues of the body. They occur when the DNA of a cell is damaged or altered and the cell begins to grow uncontrollably and become malignant. They comprise 80% to 90% of all cancers. Most breast, lung, colon, skin and prostate cancers are carcinomas (Tlsty et al., 2006).

2.2. Sarcoma

A sarcoma is a rare kind of cancer. Sarcomas are different from the much more common carcinomas because they happen in a different kind of tissue. Sarcomas grow in connective tissue cells that connect or support other kinds of tissue in body. These tumors are most common in the bones, muscles, tendons, cartilage, nerves, fat, and blood vessels of arms and legs, but they can also happen in other areas of human body.
Although there are more than 50 types of sarcoma, they can be grouped into two main kinds: soft tissue sarcoma and bone sarcoma, or osteosarcoma. Sarcomas can be treated, often by having surgery to remove the tumor (Joshi et al., 2012).

2.3. Myeloma

Myeloma is a type of cancer that develops from cells in the bone marrow called plasma cells. Bone marrow is the spongy tissue found inside the inner part of some of our large bones. The bone marrow produces different types of blood cells.

Myeloma can develop wherever there are plasma cells. So it can be anywhere there is bone marrow, including the pelvis, spine and ribcage. As it can occur in several places in the body, it is often called multiple myeloma (Slavens, 1934).

2.4. Leukemia

Leukemia is a cancer of the early blood-forming cells. Most often, leukemia is a cancer of the white blood cells, but some leukemias start in other blood cell types. There are several types of leukemia, which are divided based mainly on whether the leukemia is acute (fast growing) or chronic (slower growing), and whether it starts in myeloid cells or lymphoid cells (Winkler et al., 1999).

2.5. Lymphoma

Lymphoma is cancer that begins in infection-fighting cells of the immune system, called lymphocytes. These cells are in the lymph nodes, spleen, thymus, bone marrow, and other parts of the body. The two main types are Hodgkin and non-Hodgkin. Non-Hodgkin is the most common. The main symptom is usually an enlargement of lymph nodes that does not go away as it normally would after infection. There is no way to prevent lymphoma, but survival rates after treatment are good (Rosenberg et al., 1970).
Lymphoma is different from leukemia. Each of these cancers starts in a different type of cell.

- Lymphoma starts in infection-fighting lymphocytes.
- Leukemia starts in blood-forming cells inside bone marrow.

2.6. Mixed Cancer

Mixed cancers arise from more than one type of tissues (Chandrasekharappa et al., 1997).

3. Cancer therapy

Cancer Therapy or cancer treatment is the use of surgery, radiation, medications and other therapies to cure cancer, shrink cancer and/or stop the progression of cancer (Avendano et al., 2015).

Many cancer treatments exist. Depending on the particular situation, the patient may receive one treatment or a combination of treatments. Cancer treatment options include.

3.1. Surgery. The goal of surgery is to remove the cancer or as much of the cancer as possible (Avendano et al., 2015).

3.2. Chemotherapy. Chemotherapy uses drugs to kill cancer cells. One of its main associated problems is the nonspecific toxicity of most anticancer drugs due to their bio-distribution throughout the body, which requires the administration of a large total dose to achieve high local concentrations in a tumor. That leads to narrow therapeutic index and toxic manifestation on normal cells undergoing rapid proliferation such as bone marrow, gastrointestinal mucosa and hair (Harvey, et al. 2011). Severe vomiting, bone marrow suppression, stomatitis and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents (Harvey, et al. 2011). Another problem in cancer chemotherapy is drug resistance. After the development of a resistance mechanism in response to a single drug, cells can display cross-resistance to other structural and mechanistically unrelated drugs, a phenomenon known as multidrug resistance (MDR) (Gottesman, et al. 2002).

3.3. Radiation therapy. Radiation therapy uses high-powered energy beams, such as X-rays or protons, to kill cancer cells. Radiation treatment can come from a machine outside the body (external beam radiation), or it can be placed inside the body (brachytherapy) (Delaney et al., 2005).

3.4. Bone marrow transplant. The bone marrow is the material inside the bones that makes blood cells from blood stem cells. A bone marrow transplant, also known as a stem

cell transplant, can use the own bone marrow stem cells or those from a donor. A bone marrow transplant allows the doctor to use higher doses of chemotherapy to treat the cancer. It may also be used to replace diseased bone marrow (Pardal et al., 2003).

3.5. Immunotherapy. Immunotherapy, also known as biological therapy, uses the body's immune system to fight cancer. Cancer can survive unchecked in the body because the immune system doesn't recognize it as an intruder (Rosenwald et al., 2002).

3.6. Hormone therapy. Some types of cancer are fueled by the body's hormones. Examples include breast cancer and prostate cancer. Removing those hormones from the body or blocking their effects may cause the cancer cells to stop growing (Avendano et al., 2015; Byar et al., 1988).

3.7. Targeted drug therapy. Targeted drug treatment focuses on specific abnormalities within cancer cells that allow them to survive (Avendano et al., 2015).

3.8. Cryoablation. This treatment kills cancer cells with cold. During cryoablation, a thin, wand-like needle (cryoprobe) is inserted through the skin and directly into the cancerous tumor. A gas is pumped into the cryoprobe in order to freeze the tissue. Then the tissue is allowed to thaw. The freezing and thawing process is repeated several times during the same treatment session in order to kill the cancer cells (Bahn et al., 2002).

3.9. Radiofrequency ablation. This treatment uses electrical energy to heat cancer cells, causing them to die. During radiofrequency ablation, a doctor guides a thin needle through the skin or through an incision and into the cancer tissue. High-frequency energy passes through the needle and causes the surrounding tissue to heat up, killing the nearby cells (Cheung et al., 2005).

3.10. Clinical trials. Clinical trials are studies to investigate new ways of treating cancer. Thousands of cancer clinical trials are underway. Approximately half of cancer patients are not cured by these treatments and may obtain only a prolonged survival or no benefit at all (Avendano et al., 2015).

4. Cancer immunotherapy

Cancer immunotherapy attempts to use the exquisite power and specificity of the immune system for the treatment of malignancy. Although cancer cells are less immunogenic than pathogens, the immune system is clearly capable of recognizing and eliminating tumor cells. The immune system does more than provide protection against infections. It prevents the growth of some tumors, and some cancers can be treated by stimulating immune responses against tumor cells (Abbas et al., 2016). It may be suitable here to mention an overview of the immune system and its criteria that made us interested in this area as a field of cancer and inflammatory diseases treatment.

The immune system is one of our most complex biological systems in the body. The basic role of the immune system is to distinguish self from non-self (Patchen et al., 1987). This non-self could be an infectious organism, a transplanted organ or an endogenous cell that can be mistaken as a foreign. The immune responses of the human body against any non-self are of two types innate and adaptive (Tan et al., 2004). Innate immunity, also called natural immunity, nonspecific or native immunity, is always present in healthy individuals (hence the term innate) prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues. Phagocytes (specialized lymphocytes) called innate lymphoid cells which include natural killer (NK) cells and

several plasma proteins, including the proteins of the complement system, are parts of innate immunity mechanisms (Abbas et al., 2016).

Adaptive immunity, also called specific immunity or acquired immunity, requires expansion and differentiation of lymphocytes in response to microbes before it can provide effective defense; that is, it adapts to the presence of microbial invaders. It is more specialized and powerful than innate immune response but evolved later. Several properties of adaptive immune responses are crucial for the effectiveness of these responses, these properties include (Abbas et al., 2016).

a- Specificity and diversity as it is capable of distinguishing among millions of different antigens and the total collection of lymphocyte specificities is extremely diverse.

b- Immunologic memory as first exposure to antigen leads to primary immune response in which memory lymphocytes, which are long-lived cells, were induced. Subsequent encounters with the same antigen activate these memory lymphocytes leading to rapid, large and highly efficient responses (secondary immune responses) against the antigen.

c- When lymphocytes are activated by antigens, they undergo proliferation, generating many thousands of clonal progeny cells, all with the same antigen specificity.

d- All immune responses are self-limited and decline as the antigen is eliminated, allowing the system to return to a resting state.

e- Immune system is able react against foreign antigens but not against self-antigens.

There are two types of adaptive immunity called humoral immunity and cell-mediated immunity. Humoral immunity is mediated by proteins called antibodies, which are produced by B-lymphocytes. Secreted antibodies enter the circulation and mucosal fluids, and they neutralize and eliminate microbes and microbial toxins that are present outside host cells. Antibodies cannot gain access to cells to deal with intracellular infection or defect. It is the function of the other type, cell-mediated immunity (Abbas et al., 2016).

Cell-mediated immunity is mediated by T-lymphocytes. The antigen receptors of most T-lymphocytes recognize only peptide fragments of protein antigens that are bound to specialized peptide display molecules, called major histocompatibility complex (MHC) molecules, on the surface of specialized cells, called antigen-presenting cells (Abbas et al., 2016).

There are two main types of T-lymphocytes (Abbas et al., 2016).

- CD4 T-cells are called helper T-cells because they produce proteins called cytokines that activate many immune cells for examples help B-lymphocytes to produce antibodies and help phagocytes to destroy ingested microbes.
- CD8 T-lymphocytes are called cytotoxic T-lymphocytes because they kill cells carrying on his surface antigen that T-killer cells can recognize.

In contrast to these beneficial roles, immune responses may be away from these beneficial roles as in the following two cases:

1. Immune responses that cause tissue injury are called hypersensitivity reactions and the diseases caused by these reactions are called hypersensitivity diseases or immune-mediated inflammatory diseases. Hypersensitivity reactions may arise from uncontrolled or abnormal responses to foreign antigens or autoimmune responses against self-antigens.

Allergy or immediate hypersensitivity is caused by the activation of immune system against environmental antigens or drugs (allergens). Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis appear when the immune system loss its ability to discriminate between self and non-self antigens resulting in the immune system may attack the individual's own cells and tissues (Abbas et al., 2016). Immunosuppressants are used in treatment of autoimmune diseases and to prevent rejection of transplanted tissue. Methotrexate is effective against rheumatoid arthritis and severe psoriasis. Cyclosporine is effective in preventing acute rejection of transplanted organs and it can also be used in rheumatoid arthritis and psoriasis (Harvey, et al. 2011). Thalidomide is highly effective in treatment of autoimmune diseases.

2. In contrast, antigen recognition without adequate co-stimulation is thought to be the basis of allergy induction. Allergic cells survive but are incapable of responding to the antigen (Abbas et al., 2016). Co-stimulation is the essential process by which a second signal is delivered to naive T-cells, which facilitates their activation and the subsequent generation of an antigen-specific effect or response. It is mediated by interactions between members of the **B7** family of proteins on antigen-presenting cells and the **CD28** co-stimulatory molecule that is expressed on the surface of T-cells. This interaction, in conjunction with the primary T-cell receptor (TCR)-mediated signal, prevents the induction of immunological tolerance, which would occur in the presence of the TCR alone (Abbas et al., 2016). Cancer cells are weak immunogenic so that drugs which are able to co-stimulate T-cells can enable immune system to respond and eradicate the cancer cells without affecting normal cells. Thalidomide **1** and its analogues e.g. lenalidomide **2** and pomalidomide **3** are examples for such drugs.

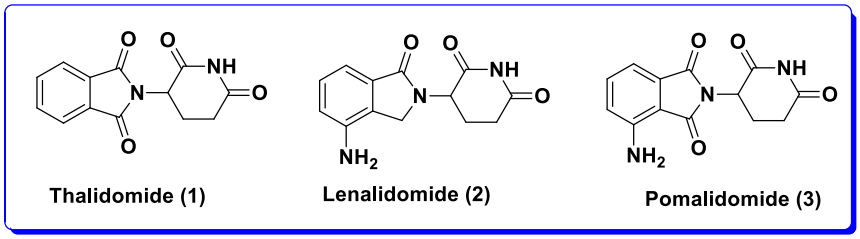


Fig. 1: Thalidomide Analogues

Thalidomide **1** is a synthetic glutamic acid derivative originally marketed as a sedative and antiemetic to provide effective relief of morning sickness during early pregnancy. The teratogenic effects associated with its use were soon discovered along with birth defects such as phocomelia and Amelia (Melchert et al., 2007). Pharmacological studies aimed at delineating the cause of thalidomide-induced teratogenicity led to the discovery of a number of unexpected pharmacological activities including anti-inflammatory, inhibition of tumor necrosis factor TNF-α production and anti-angiogenic effects (D'Amato et al., 1994). Cereblon (CRBN) has been reported to mediate the anticancer activities of thalidomide, lenalidomide and pomalidomide. Cereblon (encoded by the CRBN gene) is the substrate receptor of the cullin 4 ring E3 ubiquitin ligase complex ($CRL4^{CRBN}$), which is required for the antiproliferative activity of lenalidomide and pomalidomide in multiple myeloma (MM) cells. Cereblon also mediates the T cell co-stimulation by lenalidomide and pomalidomide (Lopez-Girona et al., 2012).

The search for thalidomide analogues with increased immunomodulatory activity and an improved safety profile led to the testing of amino-phthaloyl-substituted thalidomide analogues. These 4-amino analogues, in which an amino group is added to the fourth carbon of the phthaloyl ring of thalidomide, brought about the class termed "IMiDs". The bioactivities of the IMiDs follow the parent drug thalidomide closely, but with some increase in potency.

Lenalidomide has been approved by the US FDA in June 2006 for the treatment of relapsed or refractory multiple myeloma; its use in combination with dexamethasone was approved by the European Medicines Agency (EMA) in 2007. Notably, although side effects, such as neutropenia, remain an issue, patients treated with lenalidomide show substantially less frequent adverse effects commonly seen by administration of thalidomide.

Reports from the early 1980s onwards indicated that thalidomide was effective in the treatment of several autoimmune disorders such as rheumatoid arthritis (Gutiérrez-Rodríguez et al. 1984), cutaneous lesions of systemic lupus erythematosus and Behcet's disease (Atra, et al., 1993).
In 1998 and 1999, respectively, the US Food and Drug Administration (FDA) approved thalidomide for use in the treatment of erythema nodosumleprosum (ENL) and multiple myeloma (MM) (Tokunaga et al., 2017).

5. Development of Thalidomide

Thalidomide was developed by the Swiss pharmaceutical company CIBA in 1953 and then was introduced by the German pharmaceutical company Chemi Grunenthal in 1956 (Rajkumar, 2004). Initially marketed as Contergan, thalidomide was prescribed as a non-barbiturate hypnotic sedative able to produce deep sleep without hangover or risk of dependency. Testing in rodent models failed to establish a median lethal dose and the drug was generally believed to be nontoxic to humans (Lenz, 1988). Soon available worldwide, the drug became popular for its anti-emetic effect in pregnant woman suffering with morning sickness. Much of the drug's popularity was due to its wide availability as it was accessible without prescription and also relatively inexpensive. In Germany it quickly became a top-selling sedative and an estimated 14.6 tons were sold in 1960 (Eriksson et al., 2001).

Although the discovery of the anti-angiogenic properties of thalidomide and given its obvious clinical benefits. The use of thalidomide could present significant problems due to its teratogenic side effect. This requires intense patient monitoring during thalidomide administration. Therefore, attempts were made to synthesize thalidomide analogs that had fewer side effects than the parent compound (Bartlett et al., 2004).
As a result of these attempts, there are distinct classes of thalidomide analogues, selective cytokine inhibitory drugs (SelCIDs), Immunomodulatory drugs (IMiDs) (Marriott et al., 2001) and pleiotropic pathway modifiers (Hagner et al., 2014).

1- SelCID; compounds were reported as potent inhibitors of tumor necrosis factor alpha (TNF-α) and phosphodiesterase-4 (PDE4) and presented as potent drugs for the

treatment of inflammation, immune disorders and Crohn's disease. **CDC-801 4** (Figure 2) is a lead of the first generation series of this group and had given promising results in clinical trial phases 1 and 2 (Borges et al., 2010). In addition it is not teratogenic drugs. SelCID compounds lack T-cell co-stimulatory activity (Marriott et al., 2001).

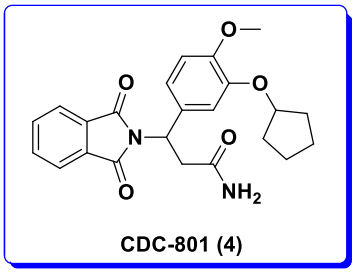


Fig. 2: Structure of **CDC-801**

2. IMiDs; Immunomodulators are agents that are intended to modify immune response in an attempt to restore immunity and/or to direct it toward tumor or pathogen in the treatment of human diseases. IMiDs represent a series of compounds that were developed by using the first-generation IMiD thalidomide as a lead compound in a drug discovery program. Thalidomide structural backbone was used as a template by chemists to design and synthesize compounds with increased immunological and anticancer properties, but lacking the toxicity associated with the parent compound (Marriott et al., 2001).

a. Initially, the rationale for developing the second-generation IMiDs in the mid-1990s was to improve the inhibition of TNF-α (Muller et al., 1996), where TNF-α regulates many cellular and biological processes such as cell differentiation, proliferation, immune responses and apoptosis (Cawthorn et al., 2008). The increased TNF-α concentration is associated with establishment and development of several diseases such as cancer and autoimmune diseases (Barbosa et al., 2011). These modifications led to the discovery of lenalidomide **2** which is a potent immunomodulator that is more potent than thalidomide as an inhibitor of TNF-α (Zeldis et al., 2011). In 2006, it was approved by FDA for treatment of MM. It has been used as successful treatment for inflammatory disorders and tumors, such as myelodysplastic syndromes (MDS), Hodgkin's lymphoma (HL) and some solid cancers (Ruchelman et al., 2013).

b. During the development of third-generation IMiDs, the emphasis in preclinical testing has changed from the anti-TNF-α activity of the IMiDs to their anti-angiogenic and immunomodulatory activities, so that; it is possible to obtain third-generation IMiDs with greater anticancer activity and/or enhanced immune responses (Bartlett et al., 2004). These modifications led to the discovery of Pomalidomide **3**, which was 10-fold more potent than lenalidomide **2** as a TNF-α inhibitor and interleukin-2 (IL-2) stimulator (Zeldis et al., 2011). It also showed better anti-angiogenic results than thalidomide **1** and lenalidomide **2** (Terpos et al., 2013). Pomalidomide was approved in February 2013 by FDA as a treatment for multiple myeloma (Dimopoulos et al., 2014).

3. Pleiotropic pathway modifiers; It was reported that, CC-122 **5** (avadomide), a new chemical entity termed pleiotropic pathway modifier, has potent anti-proliferative, immunomodulatory and anti-angiogenic activities with a potentially broader range of activity than lenalidomide **2** (Hagner et al., 2014). **CC-122 5** showed promising results in

phase I clinical trials for diffuse large B-cell lymphoma (DLBCL), MM and solid tumor (Ito et al., 2010). It was well tolerated with favorable response rates and durable remission in phase I B study on patients with B-cell Non-Hodgkin Lymphoma (NHL) (Morschhauser et al., 2017).

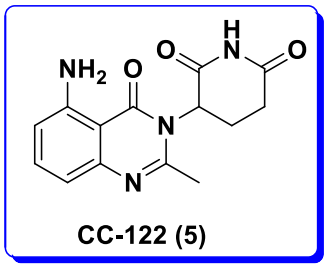


Fig. 3: Structure of **CC-122**

Cyclic imides as a class of bioactive compounds possess several biological properties such as antibacterial, antifungal, antiviral (Patil et al., 2014; Khalil et al. 2010; Azzawi et al. 2016; Dhivare et al. 2015), androgen receptor antagonistic (Patil et al., 2014), anticonvulsant, and muscle relaxant activities, analgesic (Campos et al. 2002), anti-inflammatory (Campos et al. 2002), antitumor (Yunesa et al. 2008; Noldin et al. 2015; Hassanzadeh et al. 2012; Wang ƨet al. 2017), anxiolytic (Hassanzadeh et al. 2007), antidepressive (Hassanzadeh et al. 2007). Cyclic imides and their N-derivatives contain bisamide linkages with a general structure of [-CO-N(R)-CO-]. Their hydrophobicity and neutral structures can improve crossing them of the biological membranes (Patil et al., 2014). Existence of oxygen and nitrogen atoms as donor sites can coordinate these ligands with the biological system and cause some pharmacological effects (Sultana et al. 2014; Marulasiddaiah et al. 2012). Some of these effects could be attributed to the size and electrophilic characteristics of substituent groups on the imide ring (Prado et al. 2004). Cyclic imides with a para-sulfonamide group have been introduced as potential antitubercular agents (Marulasiddaiah et al. 2012).

Cyclic imides are privileged pharmacophores and important building blocks for the synthesis of natural products, drugs, and polymers. Some of the important natural products with imide structure comprise migrastatin, lamprolobine, julocrotine, and cladoniamide A. The alkaloid phyllanthimide isolated from leaves of *Phyllanthus sellowianus* (Euphorbiaceae) has been used as a precursor for the synthesis of some of cyclic imides (Garad et al. 2015). There are several approved drugs with cyclic imide structure such as phensuximide, buspirone, and thalidomide (Kuran et al. 2010).

Although cyclic imide derivatives show wide range of biological properties, in this review, we only provide an overview on the antimicrobial activities of this scaffold and present a summary of structure–activity relationship (SAR) in some areas.

6. Naphthalimides:

Among the agents directly intercalating with DNA; naphthalimides which belong to the cyclic imides class represent an important moiety in the antitumor drug design concept (Hargreaves et al. 1970). Several biological effects suggest a potential pharmaceutical use of cyclic imides, such as antinociceptive (Andricopula et al. 1998), anti-inflammatory (Cos et al. 2001), antimicrobial (Cechinel-Filho et al. 1994), and potential antitumor agents against different cancer cell lines (Antonini et al. 2008; Matsubayashi et al. 2010). Historically naphthalimide [1*H*-benz [de] isoquinoline-1, 3-(2*H*)-diones] is considered as one of the simplest poly cyclic amides from a famous class of intercalating agents consisting of a flat, generally π–deficient aromatic or heteroaromatic system which bind to DNA by insertion between base pairs of the double helix (Li et al. 2005; Chen et al. 2010; Ott et al. 2009). The cytotoxic properties of several *N*-substituted naphthalimides are well documented to possess significant anticancer activity (Ott et all. 2011; Kamal et al. 2008). Naphthalimide derivatives exhibit their cytostatic activity through DNA intercalation, which causes enzymatic blockade and reading errors during the replication process, inhibiting both RNA and DNA synthesis and generating a multitude of reactive intermediates that result in DNA photocleavage (Qian et al. 2004; Li et al. 2004).

specially designed groups could also confer DNA sequence selectivity and allow aromatic heterocycles to position at proper sites or interact with topoisomerases so as to interfere with DNA replication and transcription (Cholody et al. 2005; Bolognese et al. 2002). DNA topoisomerase II regulates DNA topology during replication, transcription, recombination, repair and chromosome segregation. This enzyme catalyzes a DNA breakage-reunion reaction coupled to a strand passage event. Mammalian topoisomerase II is recognized as the primary cellular target of several drugs such as anthracyclines, acridines, epipodophyllotoxins and antitumor (Isabella et al. 1995).

Naphthalimide (1H-benzo[de]isoquinoline-1,3-(2H)-diones) is one of the simplest polycyclic amide consisting of a flat, generally □-deficient aromatic or heteroaromatic system. Most of the compounds having this moiety are fluorescent and exhibit broad range of biological properties such as antitumor activity against both murine and human tumor cells (Brana et al. 1995; Bailly et al. 2003; Li et al. 2011; Kamal et al. 2002; Filosa et al. 2009), antitrypanosomal (Muth et al. 2007), antiviral (Chang et al. 1993; Chanh et al. 1994), local anesthetics (Settimo et al. 1989), analgesic (Andricopulo et al. 2000), serotonin 5-HT3 and 5-HT4 receptor antagonist activity (Clark et al. 1993; Berque-Bestel et al. 2003) and as chemosensors (Duke et al. 2010) etc. Apart from this, naphthalimide derivatives have also been used in nonbiological applications like optical brighteners (Dorlars et al. 1975), nonbiological sensors (Wolfbis, 2005), fluorescent probes (Xu et al. 2010; Xu et al. 2005) and lucifer dyes (Stewart, 1978) etc. An overview of therapeutic applications of the naphthalimide-based functional materials is presented in Figure 4 (Ingrassia et al. 2009; Lv et al. 2009).

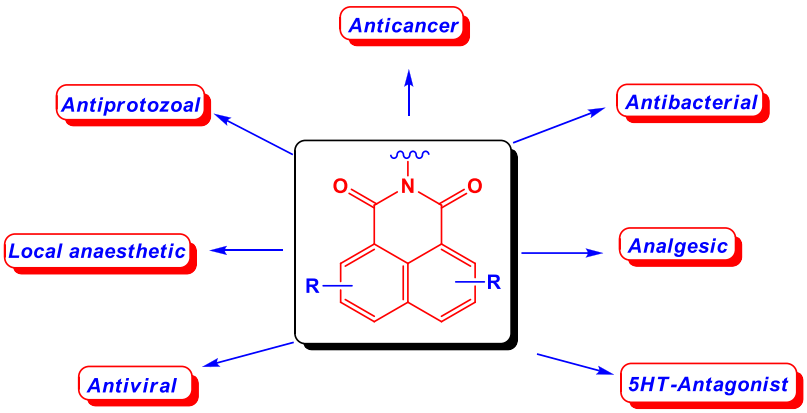


Fig. 4: Biological Activity of Naphthalimide Derivatives

Four different 3-nitronaphthalimides were synthesized with different side chains (Figure 5). These compounds showed good cytotoxic activity against HeLa and KB cancer cell lines. Two of these compounds **6** (mitonafide) and **8** exhibited potent cytotoxicity in the range of 0.5 - 1 μM. The SAR studies revealed that the presence of basic terminal group in the side chain is important and decrease in the basicity of this terminal nitrogen decreases the cytotoxicity of the molecule. Specific substitutions on naphthalimide system affect the potency to a greater extent, for example; amino, nitro or methoxy substitutions gave best results (Stevenson et al. 1984).

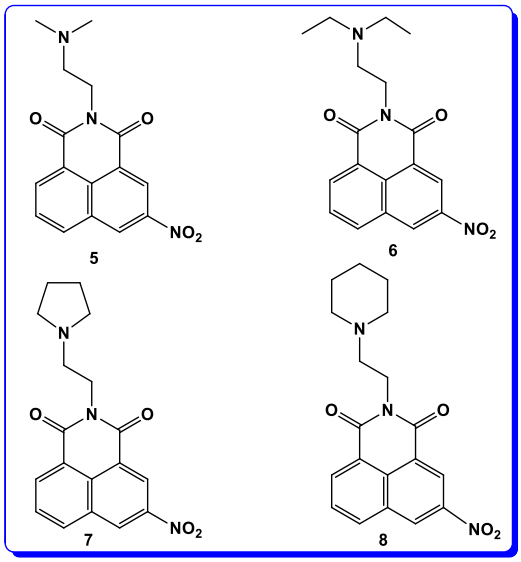


Fig. 5: First series of naphthalimides synthesized for possible antitumor activity.

Compounds **10**, **11** and **12** were designed and synthesized (Wu et al. 2009) (Fig.6). The basic hydrophilic amine chain was introduced to the N-imide position to maintain its cytotoxicity and the amino substituents were introduced to the 4-position of naphthalimide ring to avoid the side effect from N-acetylation and involve arrest of cell cycle. Their antitumor activities were evaluated against **HeLa**, **A549**, **P388**, **HL-60**, **MCF-7**, **HCT-8** and **A375** cancer cell lines *in vitro*. Most of these compounds showed comparable cytotoxicities over linalidomide against tested cancer cell lines except for **HCT-8** with the IC50 values of 10-6 to 10-5 mol/L. In most cases, the cytotoxicities increased in sequence of **12**, **11** and **10**, which indicated that the magnitude and conformation of alkyl/aryl substituents had intense influence on the cytotoxic activities of these compounds.

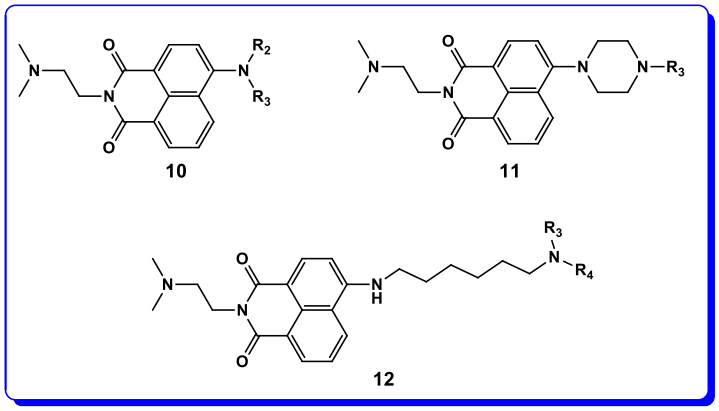


Fig. 6: Some naphthalimide derivatives

Accordingly, extensive efforts including the modification of the side chain, aromatic ring system, and the substituents on the ring have been attempted to search for more selective naphthalimide derivatives to improve the potency and reduce the adverse effects (Lv et al. 2009; Ingrassia et al. 2009). Braña et al. and Qian et al. have designed and synthesized several series of heterocyclic fused naphthalimide derivatives. They showed that some compounds exhibited better activity than amonafide (Braña et al. 2004; Li et al. 2005; Li et al. 2005; Qian et al. 2007). In the excellent paper, Qian and co-workers reported a new series of naphthalimide derivatives containing the 2-aminothiazole moiety. Among these derivatives compound **B1** (Figure 7) was found to induce expression of tumor suppressor gene **p53** in **HeLa** cells and **MCF-7** cell lines, increase the activity of **p53** and induce apoptosis in a caspase-independent manner. However, there are no studies on this kind of this kind of compounds *in vivo* (Liang et al. 2011; Liang et al. 2010).

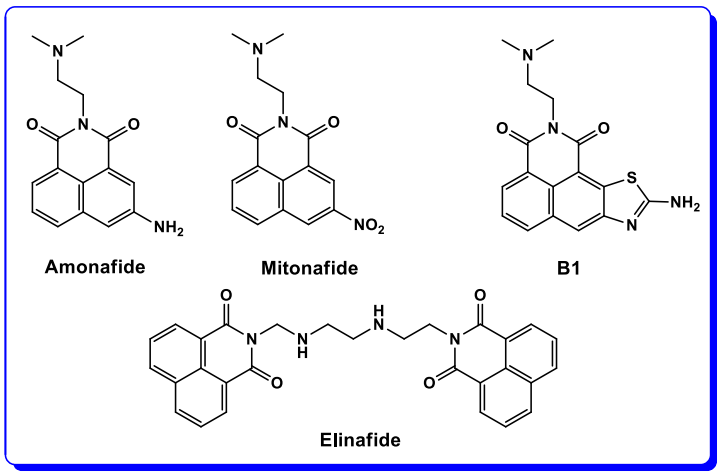
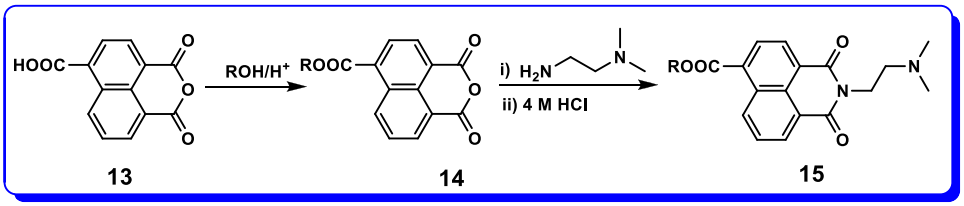


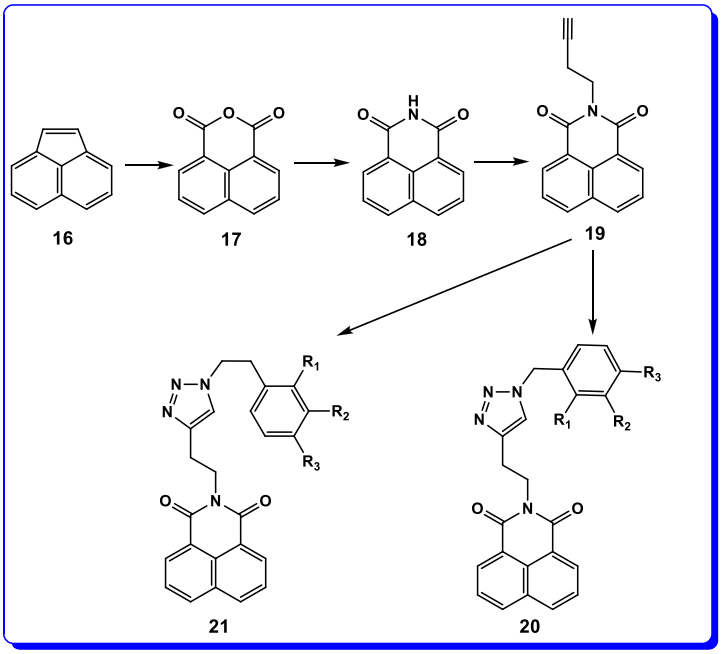
Figure 7: The structures of amonafide, mitonafide, elinafide and **B1**.

The synthesis of target compound **15** with formyl alkyl esters at the 4-position of naphthalimide was performed as shown in Scheme 1. Intermediate **13** was prepared by a modified previously reported procedure (Zhu et al. 2002; Chen et al. 2011). 4-Carboxy-1,8-naphthalic anhydride **13** was esterified with the corresponding alcohol in the presence of H_2SO_4 to afford product **14**. Product **14** was condensed with 2-dimethylethylaminoethylamine to give crude imides, which were purified by flash column chromatography. These intermediates were finally mixed with 4 M HCl at room temperature to obtain the target compound **15** as hydrochloride salts.



Scheme 1: Synthetic protocol of target naphthalimide derivatives **15**.

Furthermore, a series of novel 1,8-naphthalimide-linked 1,2,3-triazole (Zhong-Jie Xu et al. 2021) compounds were synthesized and tested for their antilung cancer activity. From the raw material acenaphthylene **16**, 1,8-naphthalic anhydride **17** was obtained by an oxidation reaction, and then the intermediate **18** was obtained by an acylation reaction. Compound **18** underwent alkylation with 4-bromo-1-butyne to yield Compound **19**, which underwent a 1,3-dipolar cycloaddition reaction with different substituted azides to obtain target Compound **20** with a 1,2,3-triazole structure, Scheme 2.



Scheme 2: Synthesis of 1,8-naphthalimide-linked 1,2,3-triazole derivatives **20**, **21**.

In general, a congeneric series of molecules should exhibit similar pharmacological profile because the interchangeable groups characterized by similar size, shape, or electronic distribution are likely to induce similar effects on binding affinities (neighbor behavior). Despite some limitations, the search for distance-mediated similarity using a quantitative measure of the pairwise relatedness between two molecules, each with multidimensional (mD) pool of attributes, contributes favorably to the ligand-based SAR practice (Bak et al. 2019).

7. Naphthalimide–amino acid and other chiral conjugates

Gunnlaugsson et al. have developed TB derivatives based on the use of short peptide based 1,8-naphthalimide derivatives, where the peptide is conjugated to the ring through the e-amino moiety. The precursors to these structures have also been found to be highly luminescent and to be active anticancer reagents with low mM activity in CML cell lines (Swagata Banerjee et al. 2013). In order to overcome the poor aqueous solubility and to achieve enhanced cellular uptake, Qian and co-workers have recently also developed related 1,8-naphthalimide based derivatives conjugated to a leucine amino acid (Wu et al. 2009). These structures, **22** and **23**, were shown to possess moderately high affinity (B104 M_1) towards ct-DNA, to bind to DNA via intercalation as shown by their increase in the viscosity of ct-DNA.

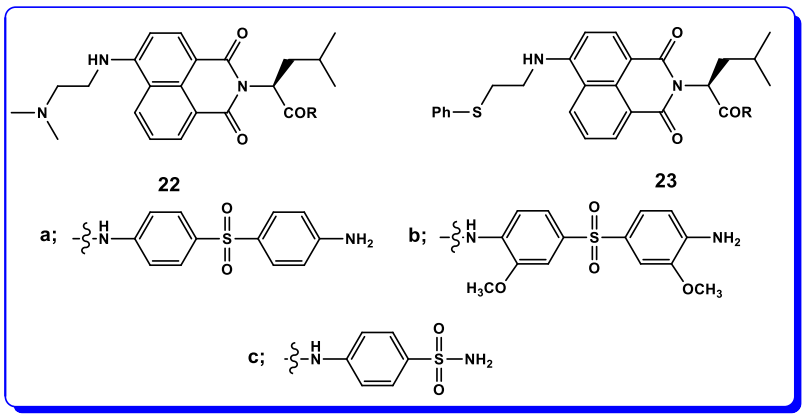


Fig. 8: Structure of 1,8-naphthalimide based derivatives conjugated to a valine amino acid.

8. Heterocyclic fused naphthalimide derivatives:

Bran˜a et al. reported the synthesis of a series of mono 1,8-naphthalimides, where the naphthalene ring was fused to a furan or thiophene ring, **24** (Bran˜a et al. 2004). The derivatives containing the furan ring, which was shown to be oriented towards the outside of the naphthalimide moiety, were found to be the most active. The dimerisation of this moiety using a polyamine linker **25** was also developed, and in line with what has been discussed above, this was found to increase the binding affinity of this structure for DNA. Dimerisation of these furano-naphthalimides also enhanced the cytotoxicity against CEM leukemia cell lines by more than 100 times compared to the corresponding mononaphthalimides (Bailly et al. 2003).

In related work, Bailly et al. showed that the bis-naphthalimide **25** exhibits different sequence selectivity with a marked preference for GC steps compared to that seen for compound **24**; which suggests that a furan ring plays a crucial role in determining the sequence selectivity (Bailly et al. 2003). It was suggested that the drug–DNA complex is stabilised by stacking and a hydrogen bonding interaction between the furan ring and the amino group of guanine. Moreover, the hydrogen bonding interactions between the protonated side chain of the ligand and O6 and N7 atoms of guanine base in the major groove act as an anchor and maintain the stability of the drug–DNA complex.

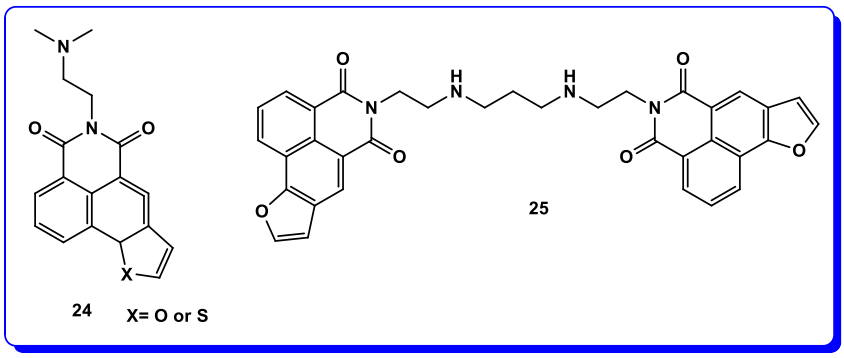


Fig. 9: Structure of heterocyclic fused naphthalimide analogues 24 and 25.

The screening results demonstrated that these derivatives displayed promising cytotoxic activity with IC 50 values ranging from 3.46 to 34.15 μM against different cancer cell lines compared with the parent compound (thalidomide).

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الملخص العربي:

في هذا المقال المرجعي نقوم بالقاء الضوء علي مرض السرطان, أنواعه ومراحله المختلفه, الطفرات الجينيه المتضمنة في حالات السرطان فضلا عن بعض المعلومات الاضافيه التي قد تكون مفيدة للكشف المبكر عن السرطان واختيار العلاج المناسب له. أيضا هذا المقال يلقي الضوء علي المخاطر الحالية والقيود علي فحص العلاج المناعي و كيف أسهمت الأبحاث الحديثة في تحديد الأمصال, المناعه الذاتية و استخدام بعض الميكروبات في المساعدة في حل هذه التحديات. أيضا يهتم هذا المقال بالعديد من الاكتشافات مثل مشابهات الثاليدويميد وخصوصا مشتقات النفثاليدوميد كمضادات للسرطان وكذلك التركيز علي مشتقات النفثاليدوميد الأحادية والمقترنه مع بعض الأمينات, الأحماض الأمينية وبعض الأنوية غير متجانسة الحلقة.

الكلمات المفتاحية : مضاد للسرطان , ايميدس , الثاليدومايد , النفثاليميدات , التوليف , السمية الخلويه