Applicability of Lipinski's Rule of Five in Drugs Used in the Treatment of Cancer

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Declaration

It is hereby declared that

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3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.
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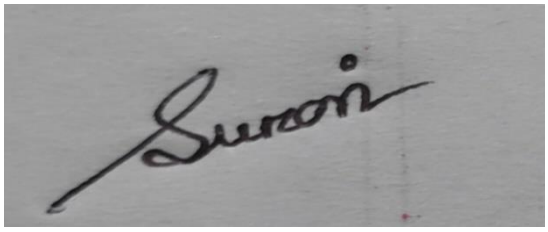

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Approval

The thesis/project titled “Applicability of Lipinski's Rule of Five in Drugs Used in the Treatment of Cancer” submitted by Snigdha Farhana Surovi (16346025) of Summer, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on August 31, 2021.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Generally, most anticancer medications are managed by an intravenous mixture. During the last decade, notwithstanding, the utilization of oral anticancer medications has expanded, on account of demonstrated adequacy and patient inclination for oral treatment. These days, most new anticancer medications are being developed are oral administration. The advancement of oral delivery is, nonetheless, frequently hampered by low and variable bioavailability influenced by physicochemical properties. The partition coefficient, molecular weight, number of Hydrogen bond donors, and number of Hydrogen bond acceptors of anticancer drugs were searched and tabulated into a Microsoft Excel spreadsheets. Drugs which do not comply with Lipinski's rule of five were identified. The types of their marketed dosage forms were checked.

Keywords: Intravenous; Bioavailability; Partition coefficient; Hydrogen bond donor; Hydrogen bond acceptor; Malignant

Dedication

I want to dedicate my project to Professor Dr. Eva Rahman Kabir ma’am and also my parents.

Acknowledgment

I would like to proceed by thanking the Almighty who is the source of our strength, knowledge, patience which have enabled me to complete this project with full diligence. It would be impossible to complete my project work without His mercy. I would like to express my deepest gratitude and appreciation to my project supervisor, Eshaba Karim (Lecturer of Department of Pharmacy, Brac University) whose expertise, ample time spent, and consistent guidance in every step providing me with her continuous support and guidance since the very first day of this journey. I would like to thank her for her great advice and patient behavior throughout this phase whenever I encountered difficulty. Moreover, I would like to thank Professor Dr. Eva Rahman Kabir, Chairperson of the Department of Pharmacy, Brac University, for allowing me to perform this project work individually and giving me the chance to work with Eshaba Karim madam. Subsequently, I would also like to thank my parents for their support and words of encouragement which motivated me to work harder to overcome the difficulties.

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List of Acronyms

STS	Soft tissue sarcomas
MM	Multiple Myeloma
UV	Ultra violate
WBC	White Blood Cell
NHL	Non-Hodgkin lymphoma
HL	Hodgkin lymphoma
HPV	Human Papilloma Virus

Chapter 1

Introduction

1.1 Literature review

Cancer is the second largest cause of death globally (Hassanpour & Dehghani, 2017). Cancer is a broad term for a set of disorders that result from aberrant cells quickly dividing and spreading to other tissues and organs. Cancer is a complicated disease characterized by multiple tempo-spatial alterations in cell physiology, which eventually result in malignant tumors. Neoplasia (abnormal cell growth) is the disease's main characteristic. (Seyfried & Shelton, 2010). It is a sickness wherein a few cells in the body are developed and partitioned rapidly and spread to different parts of the body. It can be started for many reasons anyplace in the billions of cells that make up the human body. Human cells regularly grow and duplicate (through cell division) to create new cells as needed by the body. Cells die as they become old or harmed, and new cells supplant them. This arranged interaction can sometimes deviate, bringing about variant or harmed cells developing and increasing when they shouldn't. Cancers, which are masses of tissue, can develop from these cells. Cancers could possibly be threatening to life. (Blackadar, 2016).

Malignant cancers can be infected by neighboring tissues and spread to different pieces of the body, prompting the development of new growths (a process called metastasis). Harmful growths is another name for malignant cancers. Numerous malignancies, including leukemia, create strong growths but other tumors of the blood do not create malignant growths. Harmless cancers do not infiltrate or spread into adjoining tissues. Harmless cancers or benign cancer seldom return in the wake of treatment but malignant growths which are dangerous growths do. Be that as it may, harmless cancers can develop to be very gigantic. A

few, like harmless cerebrum growths, can produce genuine indications or even be lethal. The prostate, colon and rectum, lung and bronchus, and urinary bladder all have the greatest percentages of cancer types in men. Breast cancer, lung and bronchus cancer, colon and rectum cancer, uterine corpus cancer, and thyroid cancer seem to be the most frequently occurring in women (Hassanpour & Dehghani, 2017).

How does cancer start?

The basic unit that are made up by the human body is cells. Cells are divided and extended to produce new cells as the body are requires them. Cells die when they become too old or damaged. Then, at that point, in their place, new cells appear. At the point when hereditary adjustments are being disturbed by this typical system, malignancy occurs. Cells start to multiply at a wild rate. Tumors are formed ultimately by these cells. Tumors can be life threatening or noncancerous. A harmful growth can possibly be developed and spread to different districts of the body. The expression "benign growth of tumor" alludes to a cancer that can be brought up but still do not spread. A few malignant growths do not create cancer which can be leukemia, different sorts of lymphomas, and also myeloma.

What causes cancer to spread?

The circulatory or lymphatic framework might be sent disease cells to various pieces of the body as a carcinogenic cancer develops and because of this interaction these disease cells can be duplicated and conformed extra cancers. This is alluded to as metastasis. The lymph nodes are one of the essential regions where disease spreads. Lymph nodes are little bean-molded designs. These are guided for contamination avoidance. They can be found in groups across the body, including the area of neck, crotch region, and under arms. Malignant growth might possibly go to different parts of the body through the circulatory system. The examples of

these parts are bones, liver, lungs, and cerebrum. Regardless of whether malignant growth spreads, it might be named after the part where it showed up initially.

Cancers and their types

Regardless of whether malignancies spread to different spots of the body, they are named by the space from where they originate. Malignant growth begins in the lungs and advances to the liver. There are likewise a couple of clinical wordings for various types of disease overall. Specialists characterize malignant growth into various classifications dependent on where it begins (Takahashi-Yanaga & Kahn, 2010). There are four principle types of malignancy.

Carcinomas

Carcinoma can be created on the skin or the tissue that are covering the outside of inside organ. Carcinomas are regularly strong cancers. Epithelial cells, which are covered within and outside surfaces of the body, are responsible for their development. Epithelial cells exist in various sorts when these are seen under a microscope. They frequently have a section like column. Malignancies of this class are the most far reaching. Prostate malignancy, cellular breakdown in the lungs, breast cancer, and colorectal disease are altogether instances of carcinomas. Different kinds of fibroblasts have different names under carcinoma.

Adenocarcinoma is a sort of malignant growth that happens in epithelial cells which make bodily fluid or liquids. Glandular tissues contain this kind of epithelial cell. The prostate, breast, and colon cancers are mostly recognized adenocarcinomas.

Basal cell carcinoma, a type of skin cancer that originates in the lower (base) layer of the epidermis, a person's outer layer of skin.

Squamous cell carcinoma is a kind of skin disease, created in squamous cells that are found promptly underneath the skin's surface of epithelial cells. Numerous different organs, like the

stomach, digestion tracts, lungs, bladder, and kidneys, are encircled by squamous cells. Whenever seen under a microscope, squamous cells look like level, similar to fish scales. Sometimes, squamous cell carcinomas are being called epidermoid carcinomas.

Sarcoma

The malignancy of sarcoma can occur in the tissues and bone, adipose tissues, muscles, nerves, ligaments, joints, veins, lymph, ligament. (like ligaments and tendons). It starts in the body's supporting and interfacing tissues.

Soft tissue sarcomas (STS) are an uncommon gathering of mesenchymal strong growths with heterogeneous hereditary profiles and clinical components. Nonetheless, STS are often resistant from standard treatments. It is important to further develop medicines and distinguish novel restorative targets for STS (Delgado et al., 2020).

Osteosarcoma is the most inescapable bone malignancy. The delicate tissue sarcomas are harmful fibrous histiocytoma, liposarcoma, sarcoma of Kaposi, leiomyosarcma, and dermatofibrosarcoma protuberans.

Leukemia

A type of bone marrow or blood cancer is leukemia that is characterized by an unusual growth in underdeveloped white blood cells (WBCs) known as "blasts" (Singh et al., 2017). Healthy blood cells mutate and expand uncontrollably, which causes leukemia. Solid tumors are not formed by these cancers.

All things being equal, unusual WBC (leukemia cells and leukemic impact cells) multiply and power out ordinary platelets in the blood and bone marrow. These tissue have the body's capacity to get oxygen, control draining and battle diseases. These would all be influenced by a low number of typical platelets.

Lymphomas

Lymphoma is a sort of disease that begin in the lymphocytes (T cells or B cells). These are white platelets that battle illness and are essential for the safe framework. Strange cells become accumulated in lymph nodes and lymph arteries, just as different organs, in lymphoma. Hodgkin lymphoma and non-Hodgkin lymphoma are two types of lymphoma. Various kinds of lymphocyte cells are associated with non-Hodgkin and Hodgkin lymphoma. Each type of lymphoma creates at a particular rate and reacts to treatment in an unexpected way (Lewis et al., 2020).

Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a comprehensive area that comprises a set of cancers, originate in lymphocytes and can be developed rapidly or gradually can be induced by B and T cells (Ansell, 2015).

Hodgkin lymphoma

Hodgkin lymphoma (HL) is an intermittent hematological growth portrayed by harmful Reed-Sternberg cells in a provocative climate. Patients with HL are most ordinarily analyzed in their 20s and 30s, with supradiaphragmatic lymphadenopathy with systemic B side effects. HL is profoundly treatable, even in cutting edge stages, with a blend of chemotherapy, radiation, or combined-methodology therapy (Shanbhag & Ambinder, 2018).Reed-Sternberg cells which are aberrant lymphocytes are found in people with this condition. B cells are usually the source of these cells.

Blastoma

A blastoma is cancer that develops from malignancies in precursor cells known as blasts. Depending on where in the body a blastoma is found, it is given a different name.

Nephroblastoma, for example, develops in the kidney, while retinoblastoma develops in the eye.

Blastomas are hypothesized to be the result of a genetic mistake made during embryonic development. Because blastomas originate when cells fail to grow into their ultimate kinds before or after birth, they are also known as embryonal malignancies. The embryonic tissue is then preserved. The most prevalent type of cancer in children is blastomas. They normally appear before the age of five, and many of them do so at birth.

Specific risk factors are linked to some types of blastoma. Hepatoblastoma, for example, is more common in children with certain genetic abnormalities or congenital diseases.

Myeloma

Myeloma is a medical condition that affects white blood cells. It is a disease in which monoclonal plasma cells proliferate malignantly. This cancer is the second most prevalent. A kind of blood cancer known as multiple myeloma. It begins in the spongy tissue inside bones, known as bone marrow. This is the place in the body where blood cells, including plasma cells, are produced. These cells can multiply out of control in the bone marrow, crowding out the normal, healthy cells. They can become a tumor if they accumulate. There is a growing corpus of literature that looks into the role of physical activity in all stages of multiple myeloma (prevention and survivorship), but no attempt has been made to compile and interpret it (Smith et al., 2015).

Multiple Myeloma is stunningly heterogeneous sickness, for certain patients passing on promptly after conclusion and others living for over ten years and the reason for this heterogeneity is complicated, including connections between host factors and disease biology aspects.

It is being increasingly cleared that the hidden genetic characteristics of growth cells play a key role in the clinical heterogeneity of MM (Fonseca et al., 2009).

Melanoma

Melanoma is a cancerous tumor that occurs in cells and become melanocytes, which are specialized cells that create melanin (the pigment that gives skin its color). This cancer is caused by abnormally developing skin cells. Melanomas mostly occur on the skin, yet they can likewise create in other pigmented tissues, like the eye. Most melanomas are thought to be brought about by openness to bright (UV) light from the sun, despite the fact that there is proof that some might be brought about by sunbed use. The rise of another mole or an adjustment of a current mole is the most prevalent melanoma symptom. The whole body can be influenced by this, however the back in men and the legs in ladies are the most normally influenced areas.

Melanomas are rare in sun-protected areas like the buttocks and scalp. Melanomas are typically widely spaced and multicolored. The mole may be larger than usual and scratchy or leak at times.

Risk factors

Anything that raises an individual's danger of creating disease is referred to as a malignant growth hazard factor. By and by, the overwhelming hazard factors do not cause malignant growth straightforwardly. A few group who have a few danger factors never get malignancy.

The following are some general cancer risk factors:

- rapid aging
- family history of cancer
- Using tobacco

- Obesity
- Alcohol
- Infections caused by viruses, including the human papillomavirus (HPV)
- Chemicals that are specific
- Radiation exposure, especially UV radiation from the sun

Lipinski's rule of five

Lipinski's rule of five is a rule of thumb. This criterion assists in determining whether a biologically active molecule has the chemical and physical qualities required for oral bioavailability. The Lipinski rule is based on certain molecular features for pharmacokinetic drug qualities such as absorption, distribution, metabolism, and excretion.

The Lipinski Rule of Five (Lipinski et al., 2001), which is sometimes wrongly attributed and misinterpreted, was established to enable the development of orally accessible medications, not all small-molecule pharmaceuticals. For the treatment of a variety of malignancies, oral administration is a desirable goal, but it is not a prerequisite. The Lipinski Rule's tenets (molecular weight less than 500, no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, and a partition coefficient (log P) value of less than 5) have a lot to commend them, however, they don't have to be followed to the letter for many therapeutic projects.

A compound is predicted to be a non-orally accessible medication if two or more of these conditions are violated. The term "rule of five" reflects the fact that all of the determinant criteria are multiples of five (Ivanović et al., n.d.)

Physicochemical parameters relevant to Lipinski's Rule of Five

Partition coefficients

The distribution of a solute between two immiscible solvents is described by partition coefficients. They're used as a substitute for membrane permeability and a measure of a solute's hydrophobicity in drug development. We calculate partition coefficients from transfer free energies using explicit solvent molecular dynamics simulations.

$$P = \frac{[solute]_{organic}}{[solute]_{aquous}}$$

Hydrogen bond donor

Atoms in the molecule that provides the hydrogen atom for formation of a hydrogen bond are called hydrogen bond donors.

Hydrogen bond acceptor

The atom, ion, or molecule in a molecules that participates in a hydrogen bond but that does not offer the bridging (shared) hydrogen atom are called hydrogen bond acceptors. They ususally include a strongly electronegative element, usually nitrogen, oxygen, or fluorine.

Between a hydrogen bond donor and an acceptor, a hydrogen bond is formed. The main distinction between a hydrogen bond donor and a hydrogen bond acceptor is that a hydrogen bond donor includes the hydrogen atom that participates in hydrogen bond formation, whereas a hydrogen bond acceptor contains lone electron pairs.

Molecular weight

Molecular weight is the average weight of a molecule of an element or compound measured in units once based on the weight of one hydrogen atom taken as the standard or on 1/16

(0.0625) the weight of an oxygen atom but after 1961 based on 1/12 (0.083) the weight of the carbon-12 atom; the sum of the atomic weights of all the atoms in a molecule.

1.2 Aim of the Study

The point of the investigation is to track down the anticancer drugs which do not meet the standards of Lipinsky rule of five. Lipinsky's rule of five is essentially utilized for orally administered medication. The reason for choosing anticancer drugs is because malignancy is prevalent and it is additionally a heterogeneous sickness.

Chapter 2

Methodology

The book titled ‘-‘ was used to find a list of cancer drugs. For each drug, the partition coefficient, molecular weight, number of hydrogen bond donors, and number of hydrogen bond acceptors were noted using PubChem and DrugBank. The indications of these drugs were found from the FDA label search data bank. Each indication was broken down into the histological classification of the cancer. These information were recorded in a Microsoft Excel spreadsheet.

For the data analysis, the relevant data were plotted into scattered charts. The relevant information was collected each time upon cleaning and filtering the whole data. Drugs that do not meet the criteria of Lipinski’s rule of five were identified.

Journal articles, review papers, academic books and the FDA drugs data base were used to comment on the research findings.

Chapter 3

Results

3.1 Drugs used in the treatment of carcinomas

The following table lists the relevant information.

Table 1Drugs used in the treatment of carcinoma

Sl.	Drug	logP	MW	# H Bond Donor	# H Bond Acceptor	Indication
1	Abiraterone	5.12	349.5	1	2	Prostate carcinoma
2	Anastrozole	1.58	293.4	0	4	Breast Cancer
3	Bicalutamide	2.5	430.4	2	9	Prostate carcinoma
4	Capecitabine	4.5	359.35	3	7	Colon Cancer
5	Capecitabine	4.5	359.35	3	7	Breast Cancer
6	Carboplatin	5	371.25	4	6	Advanced ovarian cancer
7	Cisplatin	-2.35	300	2	2	Testicular cancer
8	Cisplatin	-2.35	300	2	2	Advanced bladder cancer
9	Cisplatin	-2.35	300	2	2	Advanced ovarian cancer
10	Cyclophosphamide	0.8	261.08	1	4	Advanced ovarian cancer
11	Cyclophosphamide	0.8	261.08	1	4	Breast Cancer
12	Docetaxel	2.4	807.9	5	14	Metastatic gastric carcinoma
13	Docetaxel	2.4	807.9	5	14	Breast Cancer
14	Docetaxel	2.4	807.9	5	14	Non-small Cell Lung Cancer
15	Docetaxel	2.4	807.9	5	14	Prostate carcinoma
16	Docetaxel	2.4	807.9	5	14	Squamous Cell Carcinoma
17	Doxorubicin	1.27	543.5	6	12	Metastatic bronchogenic carcinoma
18	Doxorubicin	1.27	543.5	6	12	Metastatic gastric carcinoma
19	Doxorubicin	1.27	543.5	6	12	Advanced ovarian

						cancer
20	Doxorubicin	1.27	543.5	6	12	Breast Cancer
21	Doxorubicin	1.27	543.5	6	12	Metastatic thyroid carcinoma
22	Enzalutamide	4.16	464.4	1	8	Prostate carcinoma
23	Epirubicin	-0.5	543.5	6	12	Breast Cancer
24	Erlotinib	2.7	393.4	1	7	Non-small Cell Lung Cancer
25	Erlotinib	2.7	393.4	1	7	Pancreatic cancer
26	Estrogens	3.94	370.4	0	5	Breast Cancer
27	Estrogens	3.94	370.4	0	5	Prostate carcinoma
28	Etoposide	0.6	588.6	3	13	Testicular cancer
29	Etoposide	0.6	588.6	3	13	Small cell lung cancer
30	Exemestane	3.7	296.4	0	2	Breast Cancer
31	Fulvestrant	8.9	606.8	2	9	Breast Cancer
32	Gemcitabine	3.58	263.2	3	6	Advanced ovarian cancer
33	Gemcitabine	3.58	263.2	3	6	Breast Cancer
34	Gemcitabine	3.58	263.2	3	6	Non-small Cell Lung Cancer
35	Gemcitabine	3.58	263.2	3	6	Pancreatic cancer
36	Goserelin	-2	1269.4	17	16	Breast Cancer
37	Goserelin	-2	1269.4	17	16	Prostate carcinoma
38	Ifosfamide	0.86	261.08	1	4	Testicular cancer
39	Imatinib	3	493.6	2	7	Metastatic gastric carcinoma
40	Irinotecan	3.2	586.7	1	8	Colon Cancer
41	Letrozole	2.5	285.3	0	4	Breast Cancer
42	Leuprolide	1.04	1269.4	16	16	Advanced prostrate cancer
43	Melphalan	-0.52	305.2	2	4	Advanced ovarian cancer
44	Methotrexate	-1.85	454.4	5	12	breast cancer
45	Methotrexate	-1.85	454.4	5	12	squamous cell carcinoma
46	Nilutamide	1.8	317.22	1	7	Prostate carcinoma
47	Oxaliplatin	-0.47	397.3	4	6	Colon Cancer
48	Paclitaxel	3	853.9	2	14	Breast Cancer
49	Paclitaxel	3	853.9	2	14	Metastatic adenocarcinoma
50	Paclitaxel	3	853.9	2	14	Non-small Cell Lung Cancer
51	Pemetrexed	-1.5	427.4	6	7	metastatic, non-squamous, non-small

						cell lung cancer
52	Raloxifene	5.2	473.6	2	6	Breast Cancer
53	Sorafenib	3.8	464.8	3	9	Advanced renal cell carcinoma
54	Sorafenib	3.8	464.8	3	9	Metastatic thyroid carcinoma
55	Sorafenib	3.8	464.8	3	9	Unresectable hepatocellular carcinoma
56	Sunitinib	5.2	398.5	3	4	Advanced renal cell carcinoma
57	Sunitinib	5.2	398.5	3	4	Pancreatic cancer
58	Tamoxifen	6.30	371.5	0	2	Breast Cancer
59	Tamoxifen	6.30	371.5	0	2	Breast Cancer
60	Triptorelin	2.78	1311.4	17	16	Prostate carcinoma
61	Vincristine	2.82	825	3	12	Breast Cancer
62	Vinorelbine	4	778.9	2	11	Non-small Cell Lung Cancer

The following scatter plot shows the different partition coefficients of these drugs.

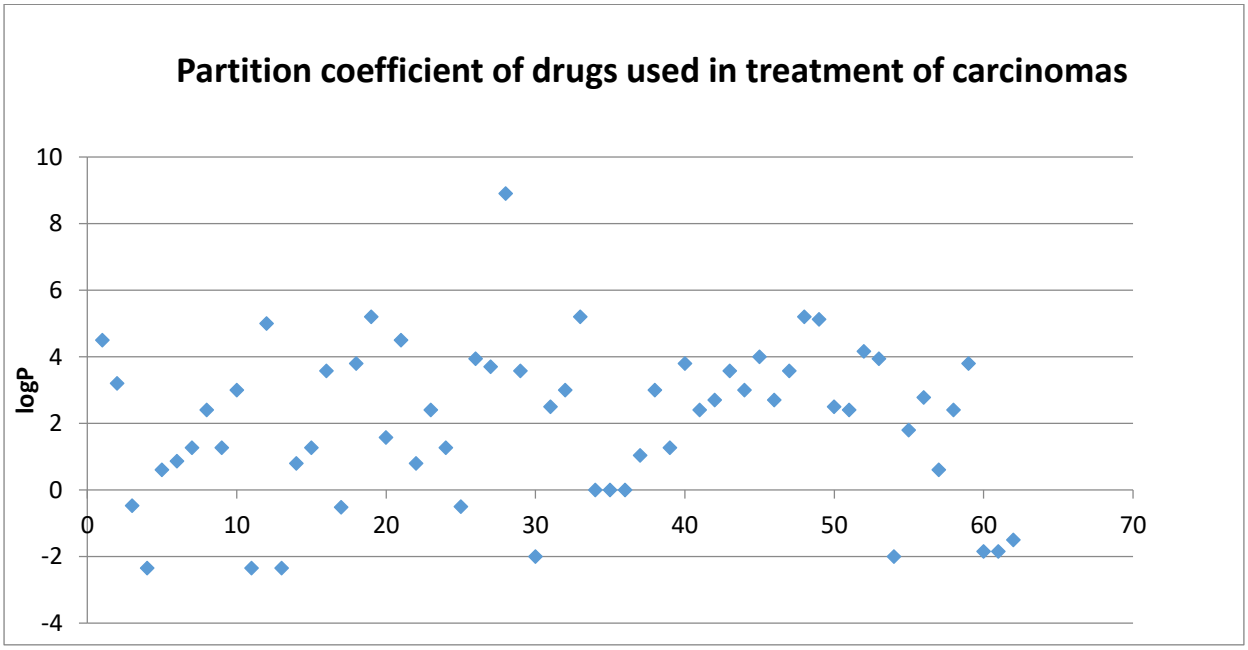

Figure 1Partition coefficient of drugs used in treatment of carcinomas

It can be seen that Fulvestrant and Tamoxifen disregard the standard of Lipinski for partition coefficient as their logP value is more than 5.

The following scatter plot shows the different molecular weight of these drugs.

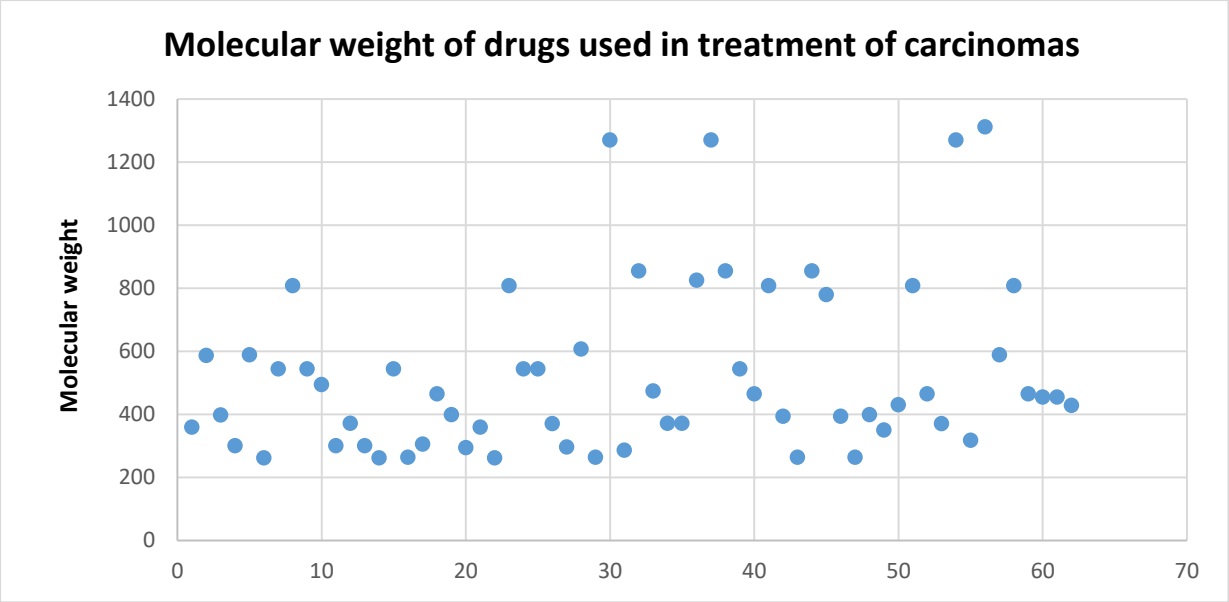

Figure 2Molecular weight of drugs used in treatment of carcinomas

It can be seen that Doxorubicin, Epirubicin, Etoposide, Fulvestrent, Goserelin, Irinotecan, Leuprolide, Paclitaxel, Triptorelin, Vincristine, Vinorelbine ignore the norm of Lipinski for molecular weight as their values are more than 500.

The following scatter plot shows the number of hydrogen bond donors of these drugs.

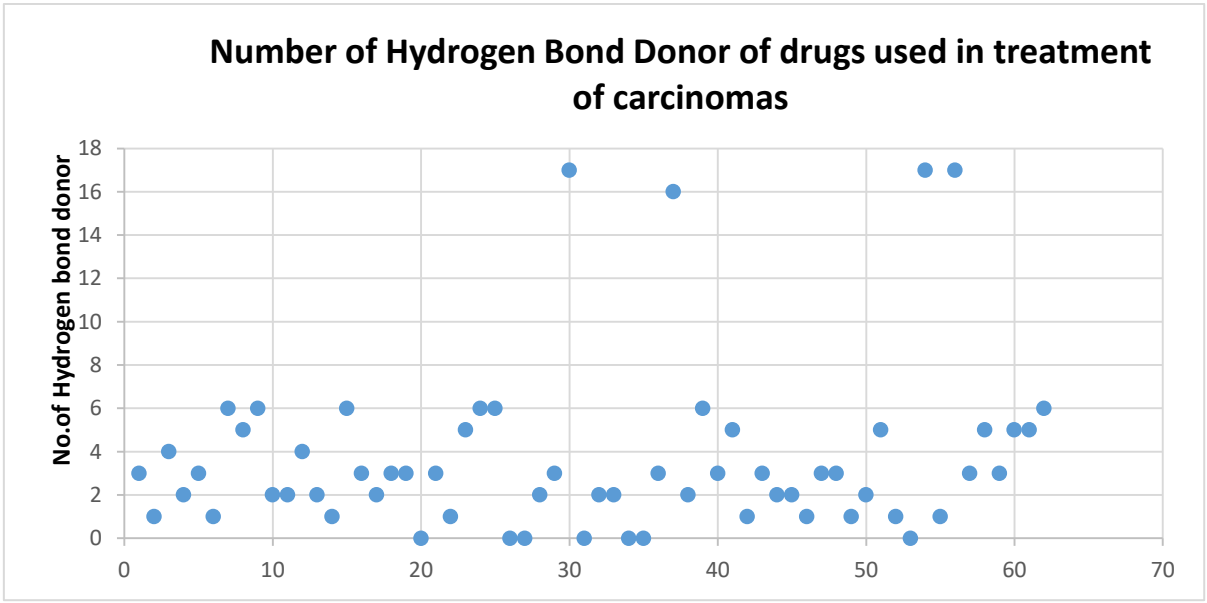

Figure 3Number of Hydrogen Bond Donor of drugs used in treatment of carcinomas

We can see that Doxorubicin, Epirubicin, Goserelin, Leuprolide, Pemetrexed, Triptorelin do not meet the Lipinski rule for the number of Hydrogen bond donors since their values are more than 5.

The following scatter plot shows the number of hydrogen bond acceptor of these drugs.

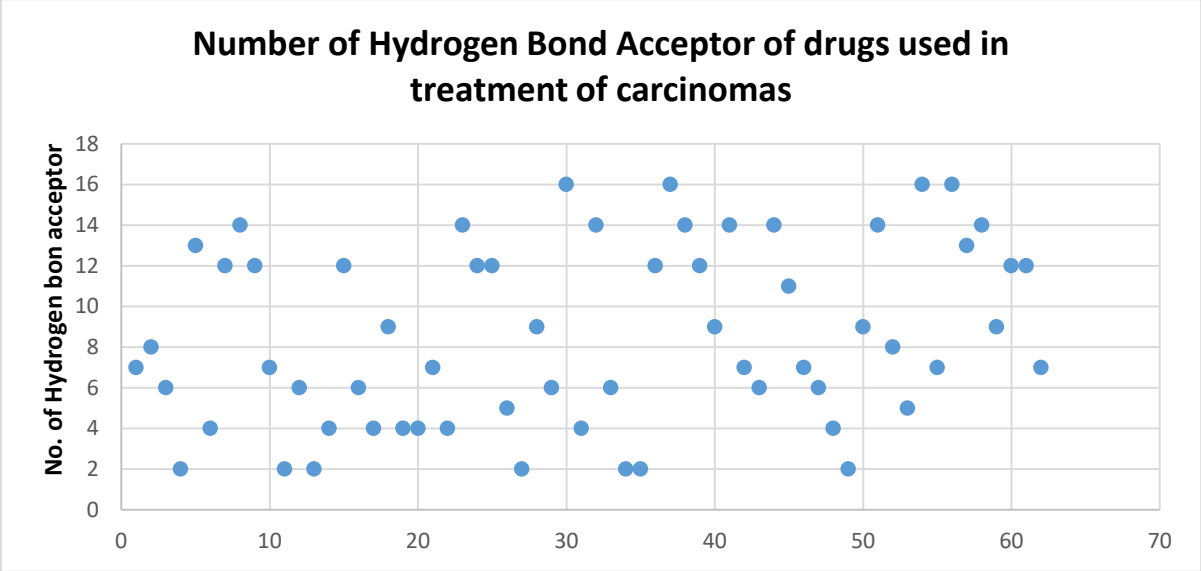

Figure 4Number of Hydrogen Bond Acceptor of drugs used in treatment of carcinomas

We can see that Docetaxel, Doxorubicin, Epirubicin, Etoposide, Goserelin, Leuprolide, Methotrexate, Paclitaxel, Triptorelin, Vincristine, Vinorelbine do not meet the Lipinski rule for the number of Hydrogen bond acceptors since their values are greater than 10.

3.2 Drugs used in the treatment of lymphomas

The following table lists the relevant information.

Table 2Drugs used in treatment of lymphomas

Sl.	Drug Name	logP	MW	# H Bond Donor	# H Bond Acceptor	Indication
1	Asparaginase		131.11	2	4	Lymphoblastic lymphoma
2	Carmustine	1.53	214.05	1	3	Hodgkin's disease
3	Carmustine	1.53	214.05	1	3	Non Hodgkin lymphoma

4	Cyclophosphamide	0.8	261.08	1	4	Mycosis fungoides
5	Cyclophosphamide	0.8	261.08	1	4	Hodgkin's disease
6	Cyclophosphamide	0.8	261.08	1	4	Lymphomas
7	Cyclophosphamide	0.8	261.08	1	4	Malignant Diseases
8	Cyclophosphamide	0.8	261.08	1	4	Non Hodgkin lymphoma
9	Dacarbazine	-0.24	182.18	2	5	Hodgkin's disease
10	Doxorubicin	1.27	543.5	6	12	Hodgkin's disease
11	Doxorubicin	1.27	543.5	6	12	Non Hodgkin lymphoma
12	Lomustine	2.83	233.69	1	3	Hodgkin's disease
13	Methotrexate	-1.85	454.4	5	12	non-Hodgkin lymphoma
14	Pralatrexate	0.51	477.5	5	11	Lymphomas
15	Procarbazine	0.06	221.3	3	3	Hodgkin's disease

The following scatter plot shows the different partition coefficients of these drugs.

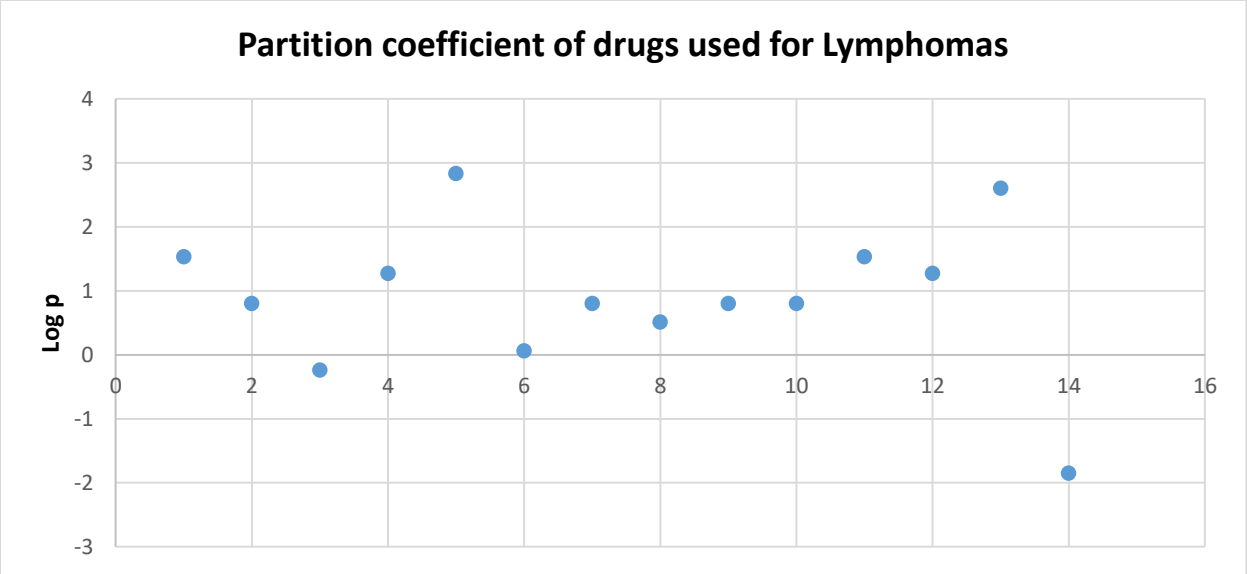

Figure 5Partition coefficient of drugs used for Lymphomas

From the Lipinski rule, we can perceive that all the drugs satisfy the guideline of the Lipinski rule for the measures of partition coefficient.

The following scatter plot shows the different molecular weight of these drugs.

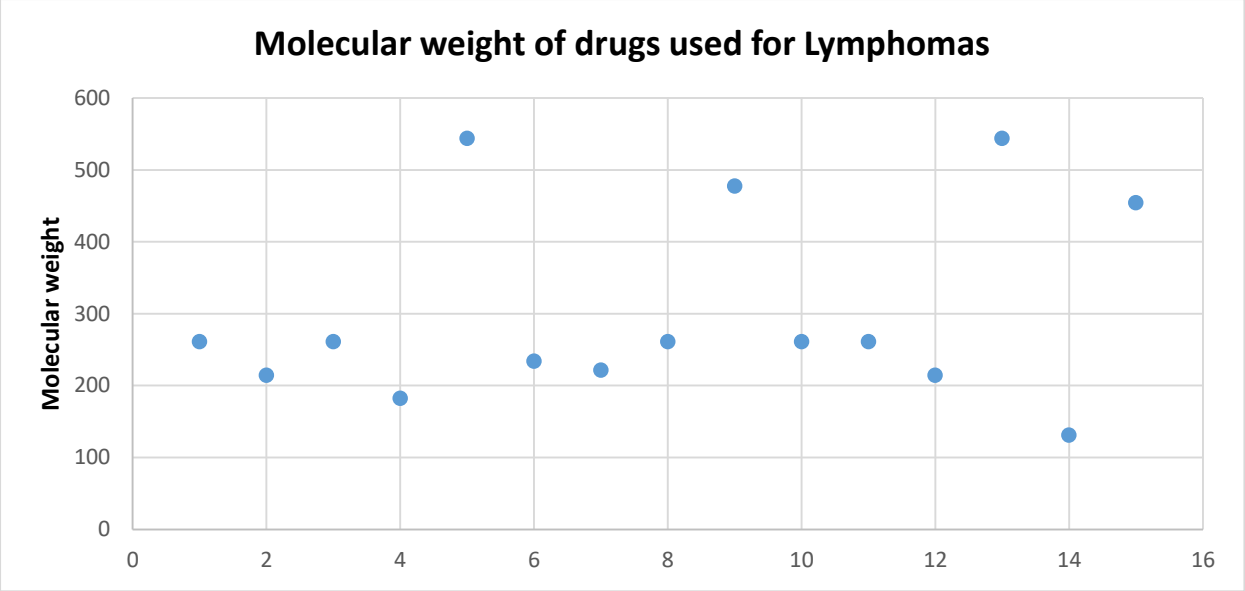

Figure 6Molecular weight of drugs used for Lymphomas

We can see that Doxorubicin violates the Lipinski requirement for molecular weight criteria because its value exceeds 500.

The following scatter plot shows the number of hydrogen bond donors of these drugs.

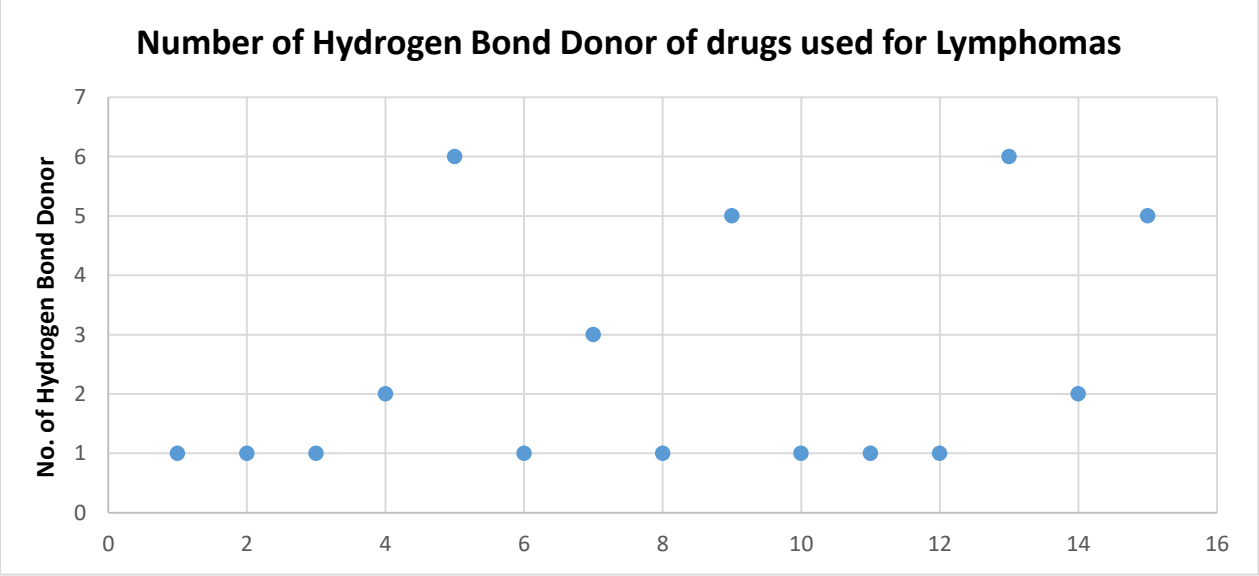

Figure 7Number of Hydrogen Bond Donor of drugs used for Lymphomas

We can perceive that Doxorubicin doesn't observe the standard of Lipinski for the rules of Hydrogen bond donors as it's value is more vital than 5.

The following scatter plot shows the number of hydrogen bond acceptor of these drugs.

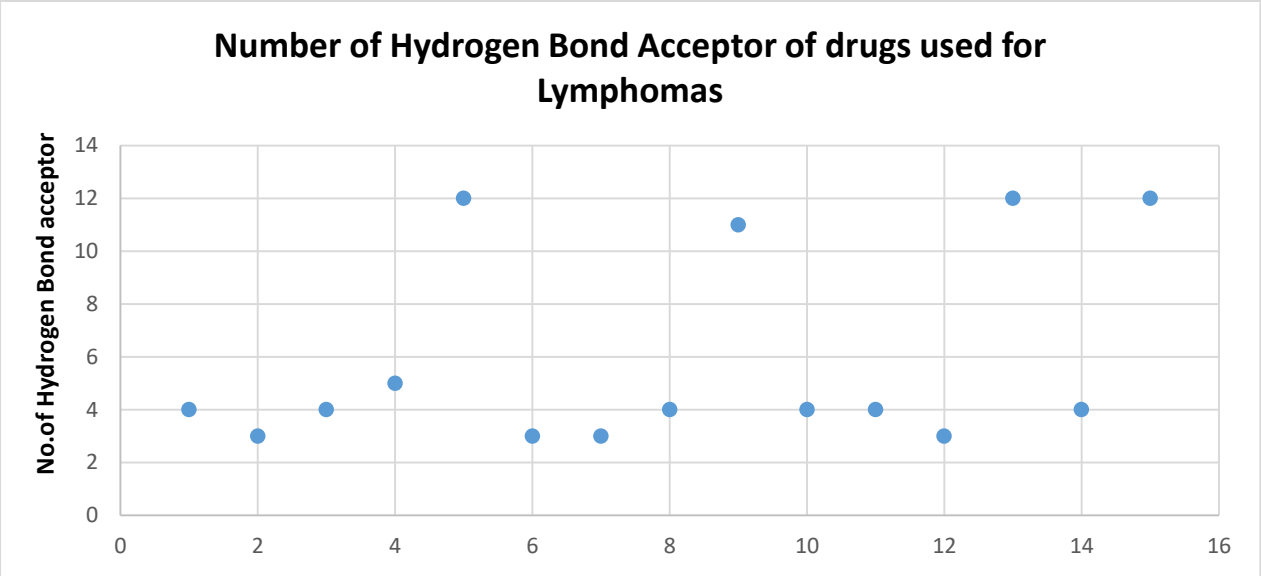

Figure 8Number of Hydrogen Bond Acceptor of drugs used for Lymphomas

It can be seen that Pralatrexate, Methotrexate, and Doxorubicin do not satisfy the Lipinski rule for the number of Hydrogen bond acceptors since their values are higher than 10.

3.3 Drugs used in the treatment of blastomas

The following table lists the relevant information.

Table 3Drugs used in tretament of blastomas

Sl.	Drug Name	LogP	MW	# H Bond Donor	# H Bond Acceptor	Indication
1	Carmustine	1.53	214.05	1	3	Brain tumors
2	Cyclophosphamide	0.8	261.08	1	4	Neuroblastoma
3	Cyclophosphamide	0.8	261.08	1	4	Retinoblastoma
4	Doxorubicin	1.27	543.5	6	12	metastatic Wilms' tumor
5	Doxorubicin	1.27	543.5	6	12	Neuroblastoma
6	Lomustine	2.83	233.69	1	3	Brain tumors
7	Methotrexate	-1.85	454.4	5	12	gestational trophoblastic neoplasia
8	Temozolomide	-2.8	194.15	1	5	Brain tumors
9	Temozolomide	-2.8	194.15	1	5	Brain tumors

The following scatter plot shows the different partition coefficients of these drugs.

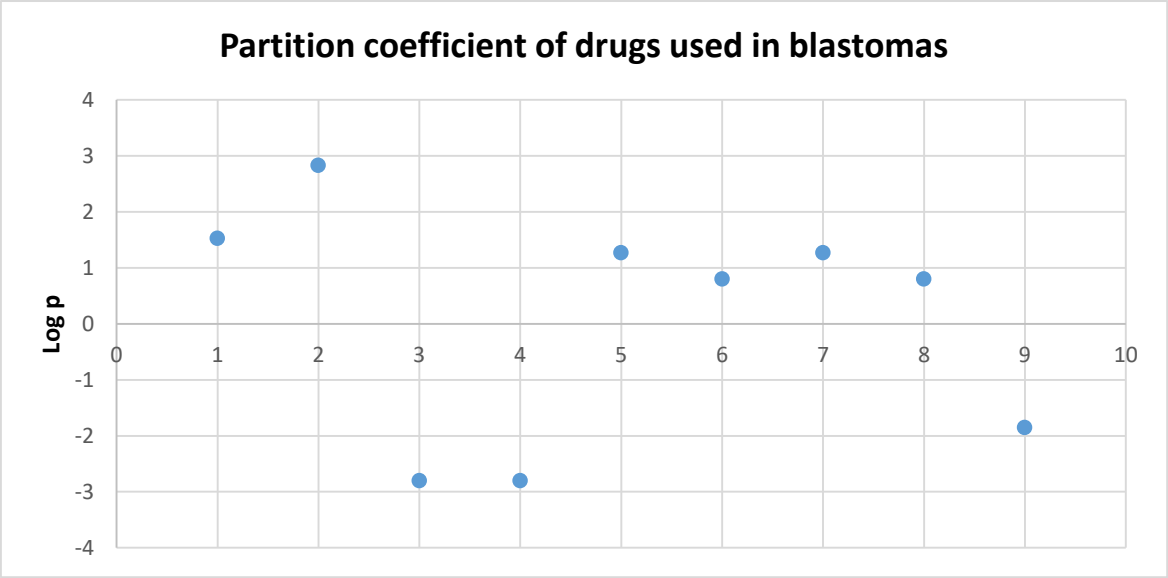

Figure 9Partition coefficient of drugs used in blastomas

It can be seen that all of the drugs fulfill the Lipinski rule's criteria for partition coefficient.

The following scatter plot shows the different molecular weight of these drugs.

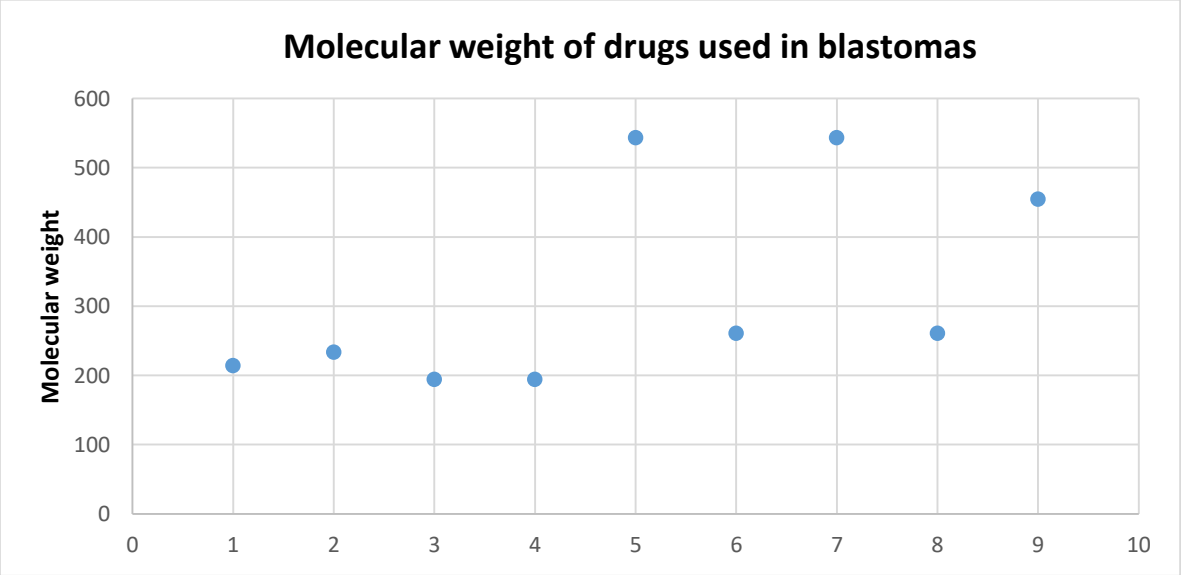

Figure 10 Molecular weight of drugs used in blastomas

We can see that Doxorubicin violates the Lipinski's rule requirement for molecular weight criteria because its value exceeds 500.

The following scatter plot shows the number of hydrogen bond donors of these drugs.

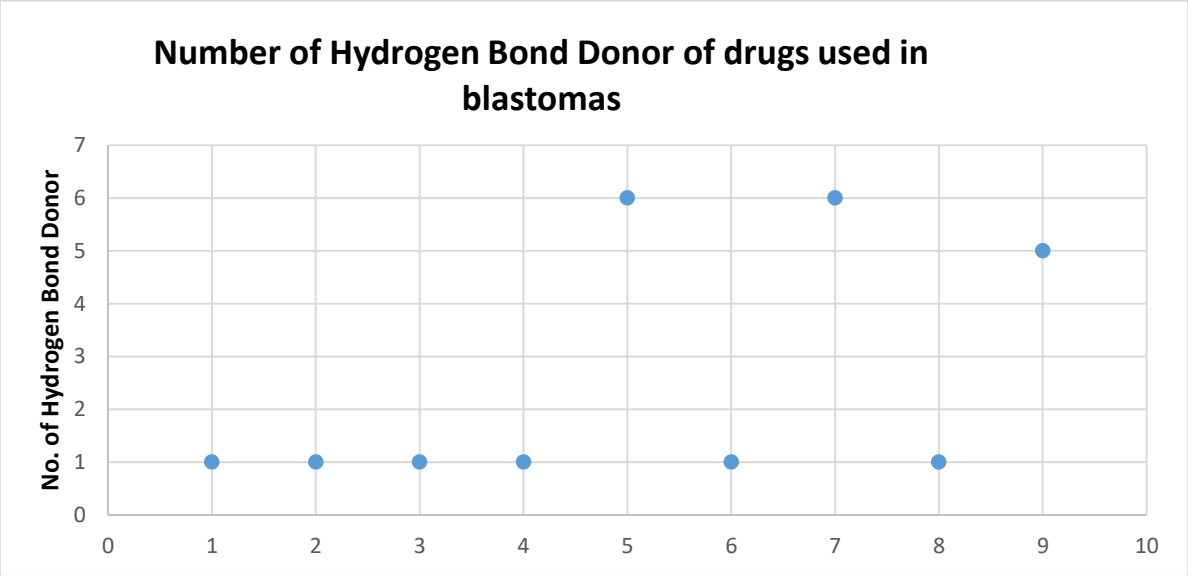

Figure 11Number of Hydrogen Bond Donor of drugs used in blastomas

It can be seen that Doxorubicin does not follow the rule of Lipinski for the criteria of Hydrogen bond donors as their value is more than 5.

The following scatter plot shows the number of hydrogen bond acceptor of these drugs.

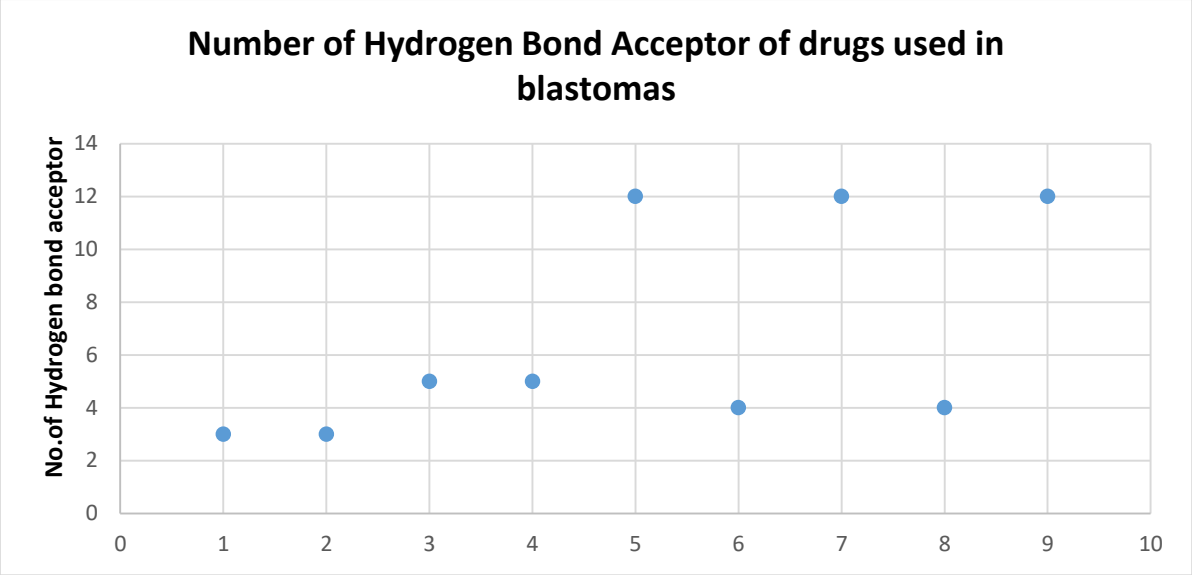

Figure 12Number of Hydrogen Bond Acceptor of drugs used in blastomas

We see from the Lipinski rule that Doxorubicin does noy follow the Lipinski rule for the number of hydrogen bond acceptors since their value is greater than 10.

3.4 Drugs used in the treatment of lymphomas

The following table lists the relevant information.

Table 4Drugs used in treatment of leukemias

Sl.	Drug Name	LogP	MW	# H Bond Donor	# H Bond Acceptor	Indication
1	Asparaginase		131.11	2	4	Acute lymphoblastic leukemia
2	Azacitidine	1.7	244.2	4	5	Refractory anemia (RA)
3	Azacitidine	1.7	244.2	4	5	FAB myelodysplastic syndrome
4	Azacitidine	1.7	244.2	4	5	Leukemias
5	Busulfan	-0.52	246.3	0	6	Leukemias
6	Cladribine		285.687	3	7	Leukemias
7	Cyclophosphamide	0.8	261.08	1	4	Leukemias
8	Cytarabine		243.22	4	5	Leukemias
9	Dasatinib	1.8	488	3	9	Leukemias
10	Daunorubicin	1.83	527.5	5	11	Leukemias
11	Doxorubicin	1.27	543.5	6	12	Leukemias
12	Fludarabine	-2.8	285.23	4	9	B-cell chronic lymphocytic leukemia

13	Idarubicin	0.2	497.5	5	10	Leukemias
14	Imatinib	3	493.6	2	7	Leukemias
15	Methotrexate	-1.85	454.4	5	12	lymphoblastic leukemia
16	Methotrexate	-1.85	454.4	5	12	meningeal leukemia
17	Mitoxantrone	-3.1	444.5	8	10	acute myeloid leukemia
18	Nilotinib	5.01	529.5	2	9	Leukemias

The following scatter plot shows the different partition coefficients of these drugs.

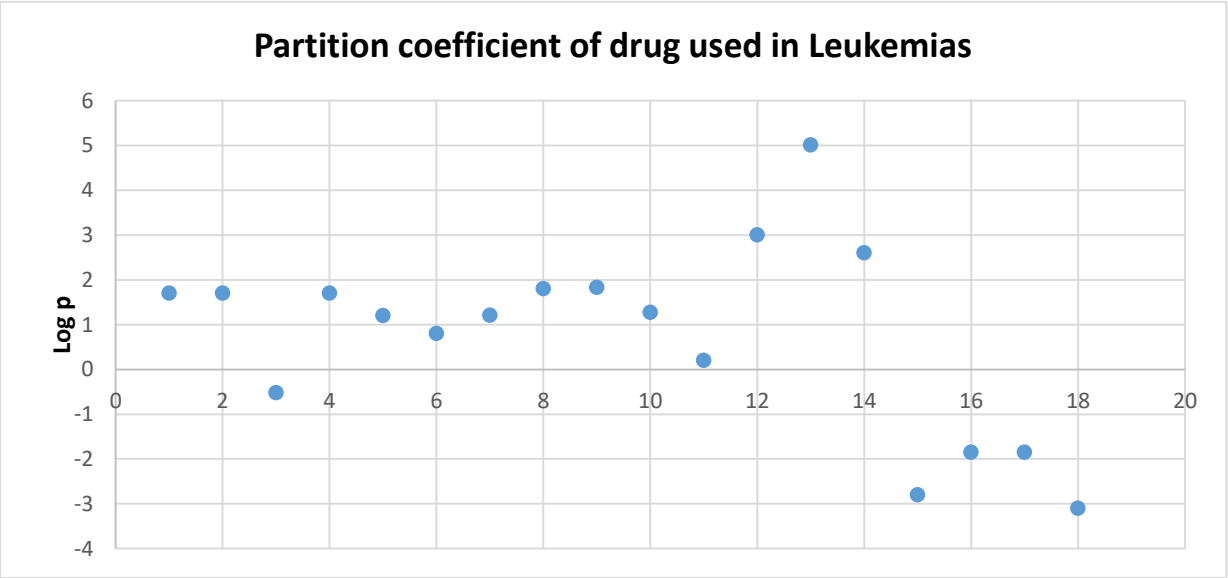

Figure 13Partition coefficient of drug used in Leukemias

It can be seen that all the drugs meet the partition coefficient criterion of Lipinski's rule.

The following scatter plot shows the different molecular weight of these drugs.

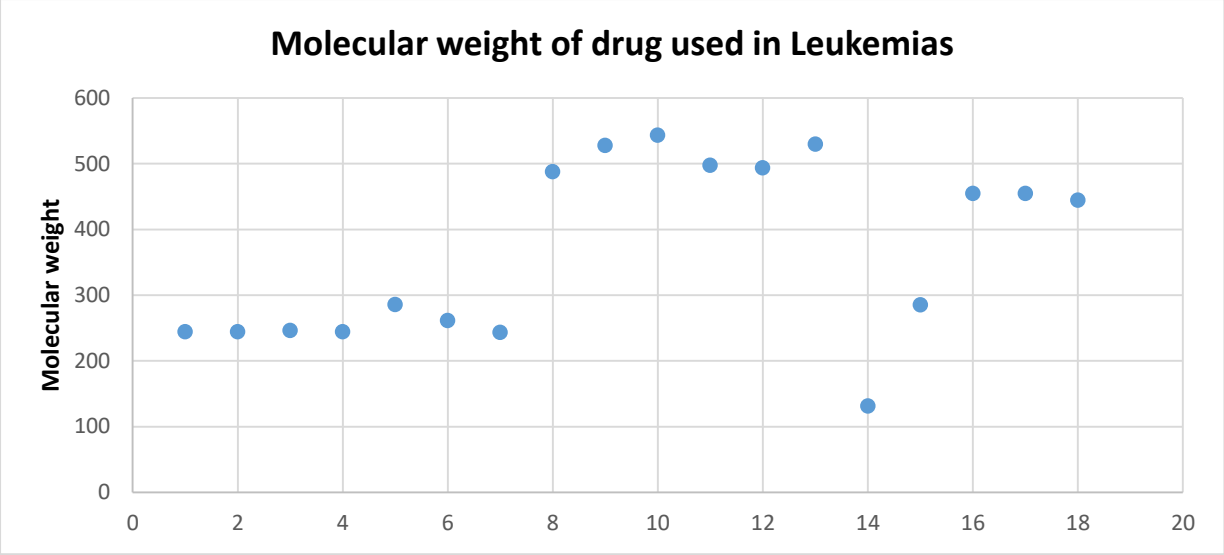

Figure 14Molecular weight of drug used in Leukemias

Doxorubicin, Daunorubicin, and Nilotinib do not follow the Lipinski rule of having molecular weight less than 500.

The following scatter plot shows the number of hydrogen bond donors of these drugs.

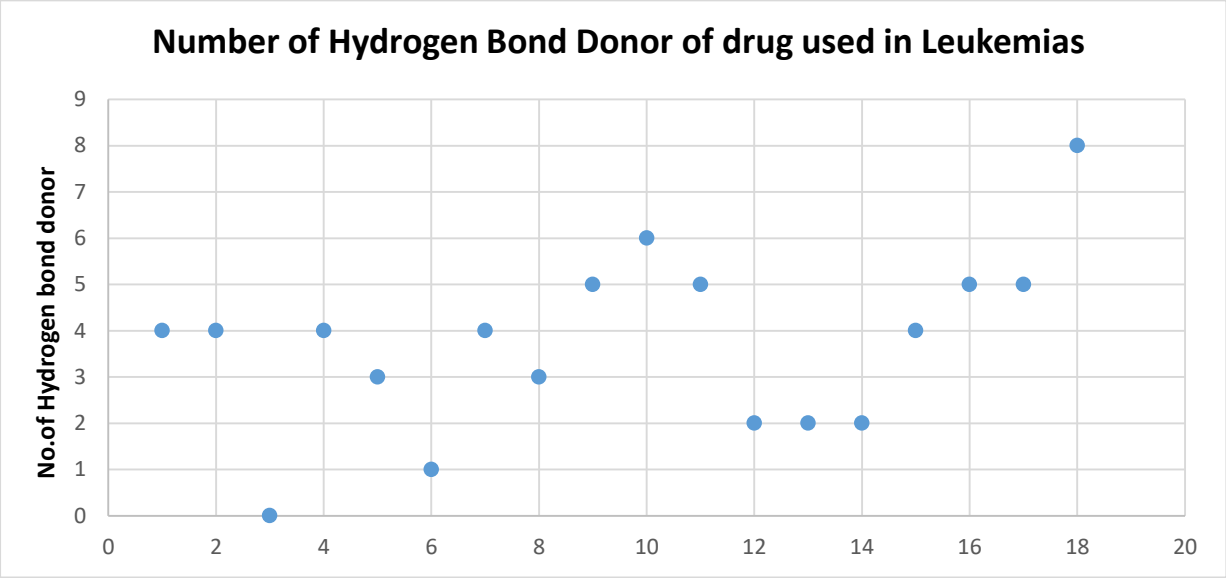

Figure 15Number of Hydrogen Bond Donor of drug used in Leukemias

It can be seen that Doxorubicin and Mitoxantrone do not follow Lipinski's rule for the number of Hydrogen bond donors because their values are greater than 5.

The following scatter plot shows the number of hydrogen bond acceptor of these drugs.

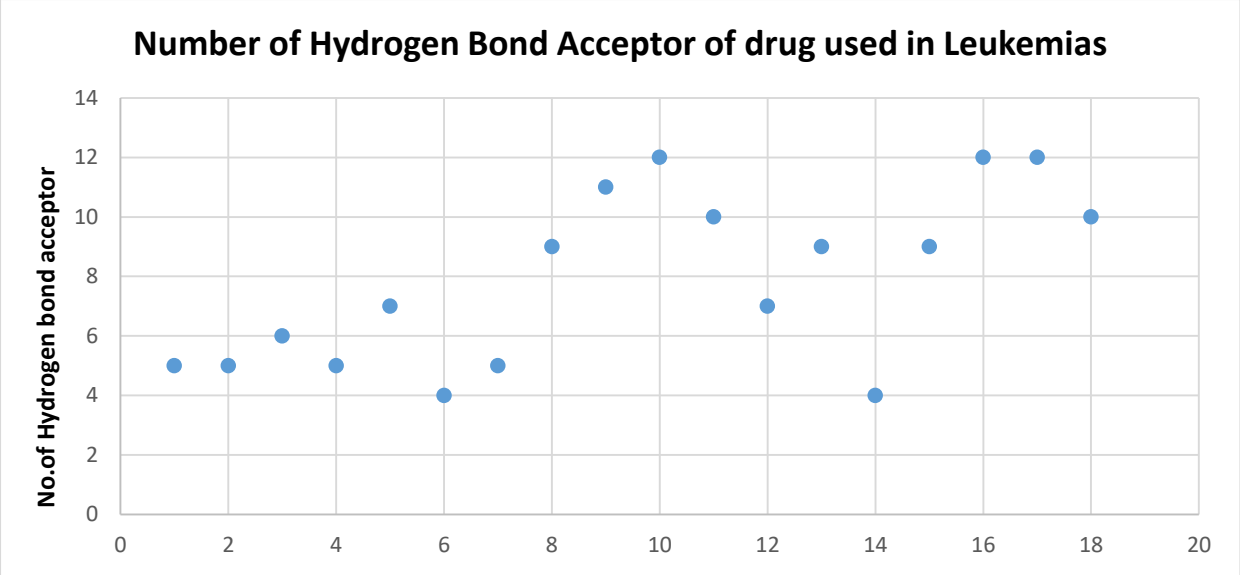

Figure 16 Number of Hydrogen Bond Acceptor of drug used in Leukemias

It can be seen that Doxorubicin, Daunorubicin and Methotrexate do not meet the criteria of Hydrogen bond acceptors under the Lipinski rule.

3.5 Drugs used in the treatment of Sarcomas, Myelomas and Melanomas

The following table lists the relevant information.

Table 5Drugs used in treatment of myelomas, sarcomas and melanomas

Sl.	Drug Name	LogP	MW	# H Bond Donor	# H Bond Acceptor	Indication	Histological site Classification
1	Carmustine	1.53	214.05	1	3	Multiple myeloma	Myeloma
2	Cyclophosphamide	0.8	261.08	1	4	multiple myeloma	Myeloma
3	Dacarbazine	-0.24	182.18	2	5	metastatic malignant melanoma	Melanoma
4	Doxorubicin	1.27	543.5	6	12	metastatic bone sarcomas	Sarcoma
5	Doxorubicin	1.27	543.5	6	12	metastatic soft tissue sarcoma	Sarcoma
6	Melphalan	-0.52	305.2	1	3	multiple	Myeloma

						myeloma	
7	Methotrexate	-1.85	454.4	5	12	osteosarcoma	Sarcoma

It can be seen that Doxorubicin do not meet the criteria for molecular weight and number of hydrogen bond donors and number of hydrogen bond acceptors as per Lipinski's rule of 5.

Chapter 4

Discussion

The following drugs were found to not meeting the Lipinski's rule of 5.

Table 6Drugs that do not follow Lipinski's rule of five

Drug Name	Cancer type	LogP	MW	# H bond donor	# H bond donor
Daunorubicin	Leukemia		X		X
Docetaxel	Carcinoma		X		X
Doxorubicin	Carcinoma Lymphoma Leukemia Sarcoma Blastoma		X	X	X
Epirubicin	Carcinoma		X	X	X
Etoposide	Carcinoma		X		X
Fulvestrant	Carconoma	X	X		
Goserelin	Carcinoma		X	X	X
Irinotecan	Carcinoma		X		
Leuprolide	Carcinoma		X	X	X
Methotrexate	Carcinoma Lymphoma Leukemia Sarcoma Blastoma				X
Mitoxantrone	Leukemia			X	
Nilotinib	Leukemia		X		
Paclitaxel	Carcinoma		X		X
Pemetrexed	Carcinoma			X	
Tamoxifen	Carcinoma	X			
Triptorelin	Carcinoma		X	X	X
Vincristine	Carcinoma		X		X
Vinorelbine	Carcinoma		X		X

Doxorubicin, Daunorubicin, Epirubicin, Docetaxel, Paclitaxel, Fulvestrant, Irinotecan, Leuprolide, Mitoxantrone, Pemetrexed, Vincristine and Vinblastine are not orally bioavailable. They are available as parenteral preparations. Etoposide is available as injectable and capsule. Methotrexate is available as injectable and tablet. Tamoxifen is

available as tablet. Therefore, at least two of Lipinski's rule of five criteria must be met to be orally bioavailable.

We could see that all the medications for myeloma meet the Lipinski rule. So, it can be said that every one of the medications utilized for myeloma is orally dynamic and these are administered through the oral route.

Because of patient preference, cheaper costs, proven efficacy, lack of infusion-related hassles, and the ability to design chronic treatment regimens, the use of oral anticancer medications has expanded over the last decade. However, oral administration of anticancer medications is usually complicated by the drug's poor bioavailability, which is associated with a large range of variability. Because most anticancer medications have a small therapeutic window and are dosed at or nearly the maximum tolerable dose, bioavailability variations can negatively affect treatment outcomes.

Several factors can help to enhance bioavailability. The dissolution rate is often the limiting step for absorption for weakly water-soluble medicines with excellent permeability. Increasing the dissolution rate is possible by adjusting the drug's formulation and physicochemical properties. Surface area can be increased by particle size reduction and enhanced wetting, while saturation solubility can be increased by adding co-solvents or changing the physical state of the drug (amorphous versus crystal form). The absorption of these medications could be improved if they were administered as a solid dispersion or as a dissolved form.

Dissolution can be expanded by the utilization of co-solvents. Low permeability is associated with considerable interpatient variability, which is problematic for drugs with a limited therapeutic window. Several attempts have been made to increase bioavailability by blocking transport proteins in the gut wall and liver for a short period. In mice with genetic knockouts

of transporter genes, pre-clinical trials revealed higher intestinal absorption of several anticancer medicines (Stuurman et al., 2013).

Several different pharmaceutical techniques are being developed to improve anticancer medication oral bioavailability. Nano suspensions, cyclodextrins, dendrimers, micelles, PEG-based nano-particles, and colloid dispersions are some of the techniques used. The majority of these methods increase drug solubility, a longer duration for the drug to stay in close contact with the absorptive membrane, or a combination of both. These approaches are currently in the preclinical stage of development, so it's questionable whether they'll make it to market and compete with current formulations.

Chapter 5

Conclusion

Malignant growth is the subsequent driving reason for mortality around the world. Generally, most anticancer medications are regulated by an intravenous mixture. During the last decade, however, the utilization of oral anticancer medications has expanded, because of proven viability and patient inclination for oral treatment. In the treatment of cancer patients, oral anticancer medicines are becoming much more widespread.

This study will help to determine the usefulness of the Lipinski rules for orally administered drugs. This information will assist with discovering oral preparations for those drugs that are currently not orally bioavailable.

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