

In vivo screening of anti-cancer inhibitors

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Abstract

The identification of effective, well-tolerated anti cancer inhibitor represents a rational chemo preventive strategy. This study has investigated the effects of naturally occurring nonprotein compounds and Topotecan and Carnosol that inhibits receptor. Our results reveal that these compounds use less energy to bind to CDK2 and inhibit its activity. Their high ligand binding affinity to the target introduce the prospect for their use in chemopreventive applications in addition they are freely available natural compounds that can be safely used to prevent lung cancer.

Key words: Enzymes, Inhibitors, Lung cancer, target drug.

Introduction

Cancer (medical term: malignant neoplasm) is a class of disease in which a group of cells display *uncontrolled growth* through division beyond normal limits, *invasion* that intrudes upon and destroys adjacent tissues, and sometimes *metastasis*, in which cancer cells spread to other locations in the body via lymph or blood^[1]. These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, and do not invade or metastasize^[3]. The presence of cancer can be suspected on the basis of symptoms, or findings on radiology. Definitive diagnosis of cancer, however, requires the microscopic examination of a biopsy specimen. Most cancers can be treated. Possible treatments include chemotherapy, radiotherapy and surgery. The prognosis is influenced by the type of cancer and the extent of disease^[2]. While cancer can affect people of all

ages the risk typically increases with age. In 2007 cancer caused about 13% of all human deaths worldwide (7.9 million) and it is projected to be 12 million deaths per year by 2030^[4].

Lung cancer

Lung cancer is a disease which consists of uncontrolled cell growth in tissues of the lung. This growth may lead to metastasis, which is the invasion of adjacent tissue and infiltration beyond the lungs^[5]. The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells.[17-23] Lung cancer, the most common cause of cancer-related death in men and women, is responsible for 1.3 million deaths worldwide annually, as of 2004^[7]. The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss^[6].

Types of lung cancer

The main types of lung cancer are *small cell lung carcinoma* and *non-small cell lung carcinoma*. This distinction is important, because the treatment varies; non-small cell lung carcinoma (NSCLC) is sometimes treated with surgery, while small cell lung carcinoma (SCLC) usually responds better to chemotherapy and radiation^[8,10].

Small cell lung carcinoma is less common. It was formerly referred to as "oat cell" carcinoma. Most cases arise in the larger airways (primary and secondary bronchi) and grow rapidly, becoming quite large^[9]. The small cells contain dense neurosecretory granules (vesicles containing neuroendocrine hormones), which give this tumor an endocrine/paraneoplastic syndrome association^[11]. While initially more sensitive to chemotherapy and radiation, it is often metastatic at presentation, and ultimately carries a worse prognosis. Small cell lung cancers have long been dichotomously staged into limited and extensive stage disease. This type of lung cancer is strongly associated with smoking.

Treatment**Surgery:**

- Blood tests and spirometry (lung function testing) are also necessary to assess whether the patient is well enough to be operated on.
- If spirometry reveals poor respiratory reserve (often due to chronic obstructive pulmonary disease), surgery may be contraindicated. Surgery is usually only an option in non-small cell lung carcinoma limited to one lung, up to stage IIIA^[12].

Chemotherapy:

- Small cell lung carcinoma, even if relatively early stage, is treated primarily with chemotherapy and radiation as surgery has no demonstrable influence on survival primary chemotherapy is also given in metastatic non-small cell lung carcinoma.
- Adjuvant chemotherapy refers to the use of chemotherapy after surgery to improve the outcome. During surgery, samples are taken from the lymph nodes. If these samples contain cancer, the patient has stage II or III disease. In this situation, adjuvant chemotherapy may improve survival by up to 15%^[13].

Radiotherapy:

- Radiotherapy is often given together with chemotherapy, and may be used with curative intent in patients with non-small cell lung carcinoma who are not eligible for surgery^[14,15].

Materials and methods:

PUBMED:

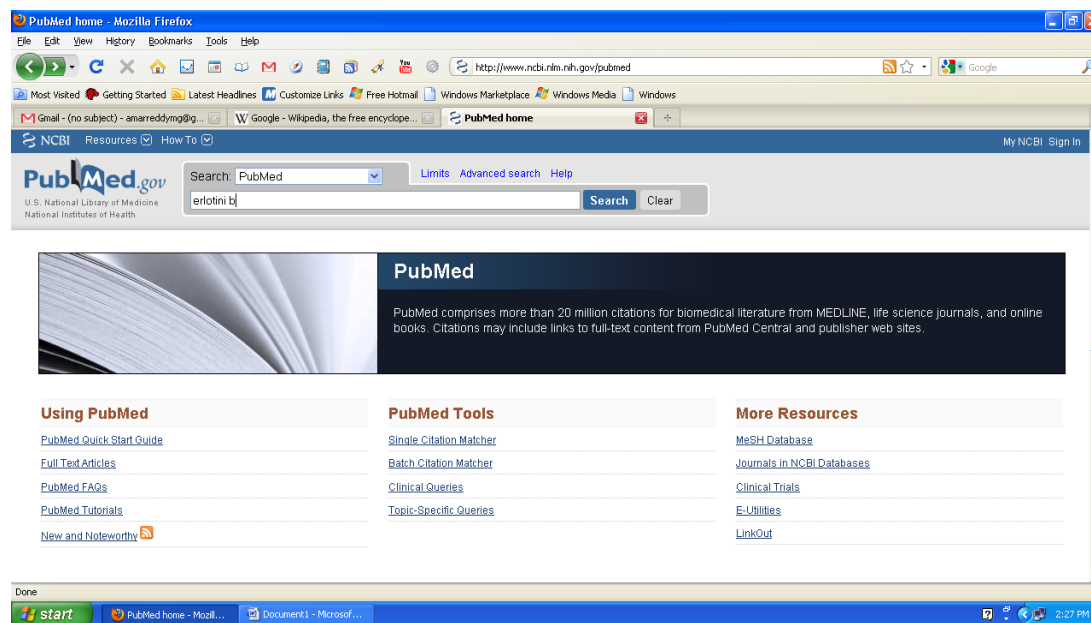


Fig 1. Pubmed snapshot

PubMed is a free database accessing the MEDLINE database of citations, abstracts and some full text articles on life sciences and biomedical topics. The United States National Library of Medicine (NLM) at the National Institutes of Health (NIH) maintains PubMed as part of the Entrez information retrieval system. Listing an article or journal in PubMed is not endorsement. In addition to MEDLINE, PubMed also offers access to

- OLDMEDLINE for pre-1966 citations. This has recently been enhanced, and records for 1951+, even those parts in the printed indexes, are now included within the main portion.
- Citations to all articles (even those that are out-of-scope, e.g., covering plate tectonics or astrophysics) from certain MEDLINE journals, primarily the most important general science and chemistry journals, from which the life sciences articles are indexed for MEDLINE.

PUBCHEM:

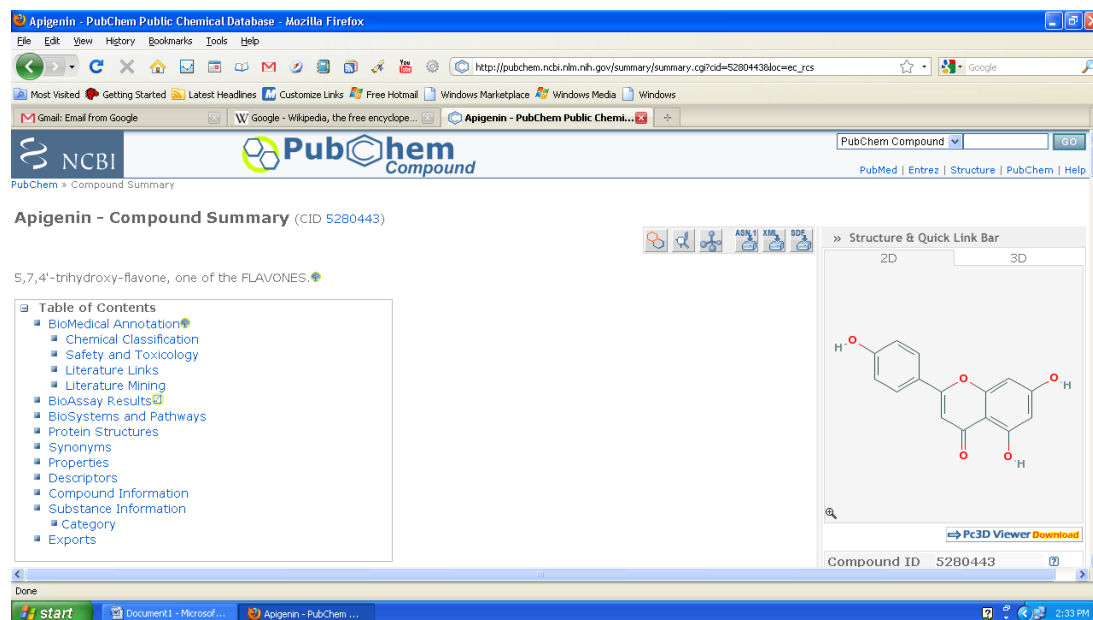


Fig. 2 Pubchem snapshot

PubChem is a database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information (NCBI), a component of the National Library of Medicine, which is part of the United States National Institutes of Health (NIH). [24-29] PubChem can be accessed for free through a web user interface. Millions of compound structures and descriptive datasets can be freely downloaded via FTP. PubChem contains substance descriptions and small molecules with fewer than 1000 atoms and 1000 bonds. The American Chemical Society tried to get the U.S. Congress to restrict the operation of PubChem, because they claim it competes with their Chemical Abstracts Service. More than 80 database vendors contribute to the growing PubChem database.[30-36]

PDB(Protein data bank):



Fig 3. pdb page snapshot

The **Protein Data Bank (PDB)** is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organisations (PDBe, PDBj, and RCSB). The PDB is overseen by an organization called the Worldwide Protein Data Bank, wwPDB.

The PDB is a key resource in areas of structural biology, such as structural genomics. Most major scientific journals, and some funding agencies, such as the NIH in the USA, now require scientists to submit their structure data to the PDB. If the contents of the PDB are thought of as primary data, then there are hundreds of derived (i.e., secondary) databases that categorize the data differently. For example, both SCOP and CATH categorize structures according to type of structure and assumed evolutionary relations; GO categorize structures based on genes. [37-45]

Results:



Fig1.TOPOTECAN structure retrieval from Pubchem

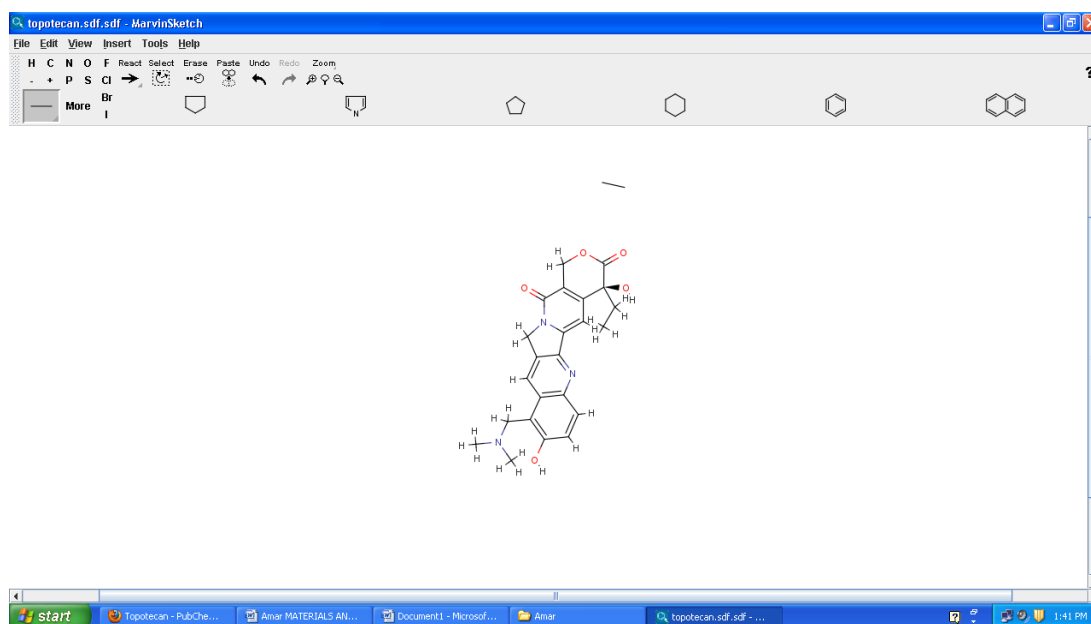


Fig 2. Structure of TOPOTECAN in PUBMED

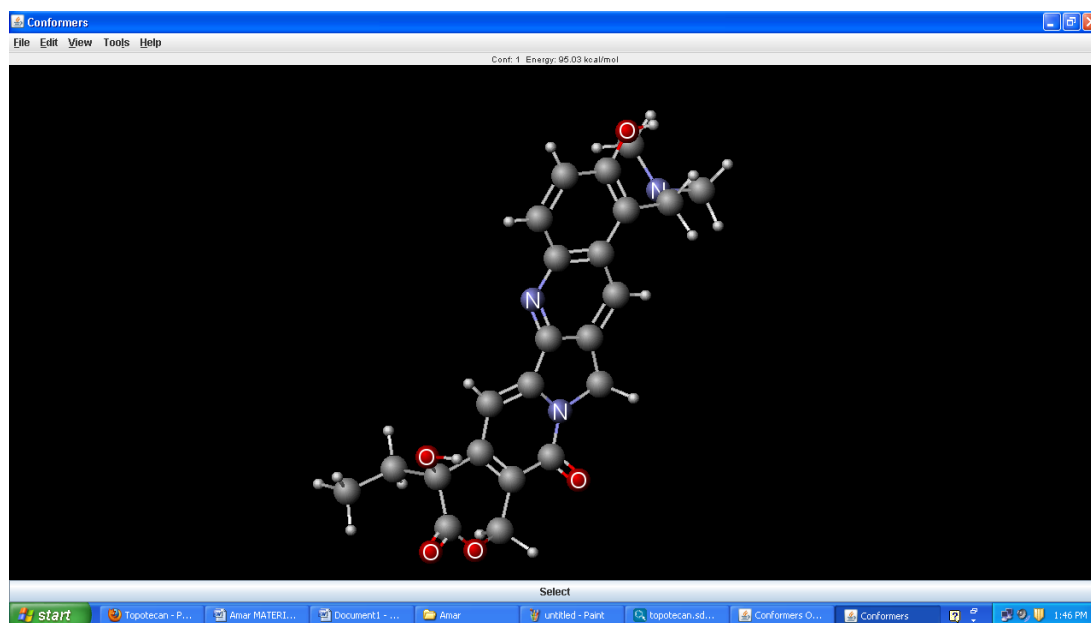


Fig 3. Shows 3d Structure with Energy Value

Docking score value:

sno	Name of the molecule	G-value
1	acetogenins	-17.69
2	Allicin	-14.17
3	Allixin	-13.98
4	allylsulphides	-10.68
5	Apigenin	-19.62
6	Artesunate	-21.57
7	Betaglucan	-14.66
8	Capsaicin	-19.75
9	Catechin	-18.35
10	Combretastatin A-4	-20.23
11	Diallyl disulfide	-12.60
12	Ellagic acid	-17.54
13	Ferulic acid	-17.83
14	Glutathione	-12.78
15	Hydroxytyrosol	-12.60

Discussion

Around 100 small molecules from different categories such as Alkaloids, Flavanoids, Tannins and glycosides were taken as targeting agents that are responsible for inhibiting the biological processes important in causing cancer. The investigational drug i.e (Erlotini b) which is under clinical trial was used as a reference drug in this study. Since cancer pathways was mainly responsible for causing cancer, we took it as our target protein and structure for the same was retrieved from PDB. Initial screening of the molecules was based on Lipinski's rule of five. The molecules which satisfy the criteria were subjected to receptor-ligand interaction study using docking tool such as Quantum 3.3.0. Molecules which showed better interactions with CDK 2 than reference drug were considered and subjected to one more docking tool i.e. Quantum, a commercial tool for finding Receptor-ligand interaction and docking score was considered for further result interpretation.[40-45]

Summary

In our study attempt was made to find potent anti-cancer inhibitor for Chemokine receptor using natural agents targeting biological processes important in cancer. One group of cancer receptors critically implicated in lung cancer (Chemokine) is served as a molecular target for our study. The investigational anti-cancer inhibitor Erlotinib was considered as a reference drug in this work. Hundreds of natural molecules were selected from various scientific articles. The initial screening of the molecules based the lipinski's rule of five. Molecules which were satisfying this rule were taken for receptor-ligand interaction study using docking tools Quantum. After the docking process, the molecules were subjected to raking process.

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