# Prediction of Biological Activity Spectra for Few Anticancer Drugs Derived from Plant Sources

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## ABSTRACT

Over the past decade plants have become an interesting source of new classes of pharmacologically active natural products. Some secondary metabolites are also well known for their effectiveness on living species. The PASS (Prediction of Activity Spectra for Substances) computer program, which is able to simultaneously predict more than one thousand biological and toxicological activities from only the structural formulas of the chemicals, was used to predict the biological activity profile of 7 secondary metabolites. PASS predictions were successfully compared to the available information on the pharmacological and toxicological activity of these compounds.

## INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external factors (tobacco, chemicals, radiation, and infectious organisms) and internal factors (inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote carcinogenesis. When the control signals in one of the cell goes wrong, and its life cycle becomes disturbed, it divides and divides. It continues multiplying uncontrollably, and the result of this accumulation of abnormal cells is a mass of cells called a "tumor". A tumor can be either benign or malignant.

Benign tumors are non-cancerous and are rarely life-threatening. They do not spread (metastasize) to other parts of the body. Many breast lumps, for example, are benign tumors.

Malignant tumors are cancerous and can spread to other parts of the body. When a malignant tumor spreads, the malignant cells break off and travel through the blood lymph system to other places in the body to settle and multiply; or metastasize, resulting in a new tumor called a secondary tumor, or metastasis. The name given to the cancer, however, is reflective of the origin of the cancer, even if it has spread to other areas of the body. For example, if prostate cancer has spread to the liver it is called metastatic prostate cancer.

Ten or more years often pass between exposure to external factors and detectable cancer. Cancer is treated with surgery, radiation, chemotherapy, hormone therapy, biological therapy, and targeted therapy. As it is difficult to differentiate between the cancerous and normal cells in-vivo the innovation of a potential drug against the disease it

yet a menace. With the known therapeutic knowledge and indigenous crude custom scientists have been thriving their excellence in the field of pharmacology to design a potential drug that is suited to kill the cancerous cells alone.

Most anti-cancer drugs act by inhibiting DNA synthesis or some other process in the cell growth cycle. Because anti-cancer drugs generally affect rapidly dividing cells, other non-cancerous cells will also be affected. The way in which the other cells are affected determines the side-effects of the individual drugs. Other cells affected include blood cells, which fight infection, help the blood to clot, and carry oxygen to all parts of the body. When blood cells are affected, patients are more likely to get infections, may bruise or bleed easily, and may feel unusually weak and very tired. Rapidly dividing cells in hair roots, and cells that line the digestive tract, may also be affected. As a result, side effects may include loss of hair, poor appetite, nausea and vomiting, diarrhea, or mouth and lip sores. Many of these side effects can now be controlled, thanks to new or improved drugs. Side effects generally are short-term and gradually go away. Hair grows back, but it may be different in color and texture. With the known ethno botanical knowledge and phytochemical interpretations there are a number of drugs that could be effective against the cancer. The outcome of insilico knowledge on the designing of drug is yet another boom for the designers to minimize the work, PASS (*Prediction of Activity Spectra for Substances*) is one such a server that predicts the possibility of a drug to be active against a target based on thephysico- chemical methods using comparisons and various algorithms.

PASS predicts simultaneously several hundreds of biological activities (pharmacological main and side effects, mechanisms of action, mutagenicity, carcinogenicity, teratogenicity and embryotoxicity). The biological activity spectrum of a compound presents all compounds' actions despite the difference in essential conditions of its experimental determination. If the difference in species, sex, age, dose, route, etc. is neglected, the biological activity can be identified only qualitatively. Thus, "the biological activity spectrum" is defined as the "intrinsic" property of a compound depending only on its structure and physico-chemical characteristics.

PASS is the product of ideas originated more than 25 years ago within the framework of the National Registration System of New Chemical Compounds organized in the USSR in 1972 (Burov *et al*., 1990). It was V.Avidon who suggested that many kinds of biological activity could be predicted on the basis of structural formulae of chemical compounds (Avidon, 1974). Similar approach was under development by V.Golender and A.Rozenblit (Golender, and Rosenblit, 1983). PASS has already found new leads with antiulcer, antitumor and antiamnestic activity, and discovered new mechanism of action for some compounds with known effect (Filimonov and Poroikov, 1996, Filimonov *et al.,* 1995, Poroikov and Staraya Kupavna, 1995, Poroikov *et al.,* 1996, Poroikov *et al.,* 1994). Experimental determination of drug efficacy and safety is time- and cost-consuming procedure. There exist standard tests for drug safety assessment (Maggon *et. al.*, 1992) and different strategies for search of new lead compounds (Walker, 1994). Biological testing is organised taking into account "similarity/dissimilarity" of new compound to the other known biologically active substances. Several similarity/dissimilarity suggestions are used both in drug design and screening to determine if particular tests are necessary and sufficient for comprehensive estimation of new compound activity. PASS 4.20 training set includes 9314 biologically active substances. PASS 4.20 predictsthe probabilities of presence/absence for 114 biological actions simultaneously (main and side pharmacological effects, mechanisms, specific toxicity). It is shown that the approach, used in PASS, can be applied to the other biological activities [Filimonov *et al.,1995,* Shilova *et al.,*, Filimonov *et al.,1996*].In the past years Computer Aided Drug Design (CADD) is widely used in new drug R & D [Franke and Herrmann, 1994]. Recently, we developed the computerised system PASS (Prediction of Activity Spectra for Substance) that estimates simultaneously the

probability of more than 100 pharmacological effects and mechanisms [Filimonov *et al, 1995,* Filimonov and Poroikov (1996)]. The effectiveness of this computer aided approach application in screening has been shown to be 800% more than the random guess-work [Filimonov and Poroikov (1996)] and 300% more than the estimation by skilled experts [Poroikov *et al*., 1993]. However, the antiulcer action has not been covered by the initial version of PASS. Therefore, in this work we extend PASS prediction's area on antiulcer activities and use this specialised system to discover some new antiulcer agents.

Prediction of this spectrum by PASS is based on SAR analysis of the training set containing more than 35,000 compounds which have more than 500 kinds of biological activity (http://www.ibmh.msk.su/PASS). Therefore, PASS once trained is able to predict simultaneously all biological activities which are included in the training set. To provide the best quality of prediction new information about biologically active compounds is collected permanently from papers and electronic sources and, after the experts' evaluation, is regularly added to the training set.

## MATERIALS AND METHODS

The following chemical compounds were selected for the study, the predicted structures are obtained from the Pub-Chem database of National Center for Biotechnology Iinformation.

### 1. Taxol

Belongs to the family of drugs called mitotic inhibitors. It is obtained via a semi-synthetic process from *Taxus baccata* and other species of Taxus (Yew trees). It is approved for treating certain cancers like breast cancer, ovarian cancer, and lung cancer.

### 2. Vinblastine

Belongs to the family of plant drugs called vinca alkaloids. It is a mitotic inhibitor. Vinblastine alkaloid is extracted from *Catharanthus roseus*. It is used in the treatment for some types of cancer including leukaemia, lymphoma, breast and lung cancer.

### 3. Vincristine

Belongs to the family of plant drugs called vinca alkaloids. Vincristine alkaloid is extracted from *Catharanthus roseus*, belonging to the family Apocynaceae. This species is also known as *Vinca rosea* and has the alternative common name of Vinca. Vincristine is an alkaloid derived from flowering periwinkle. Vincristine is used as a chemotherapeutic agent for some types of cancers including leukaemia, lymphoma, breast and lung cancer.

### 4. Topotecan (a camptothecin derivative)

Belongs to the family of drugs called topoisomerase inhibitors. It is also called Hycamtin. Camptothecin, a quinoline-based alkaloid is isolated from *Nothapodytes foetida*. It has been approved for ovarian cancer therapy.

### 5. Irinotecan

Belongs to a family of drugs called topoisomerase inhibitors. It is a camptothecin analog and isolated from *Nothapodytes foetida*. Also called CPT 11. It is approved for metastatic colorectal cancers.
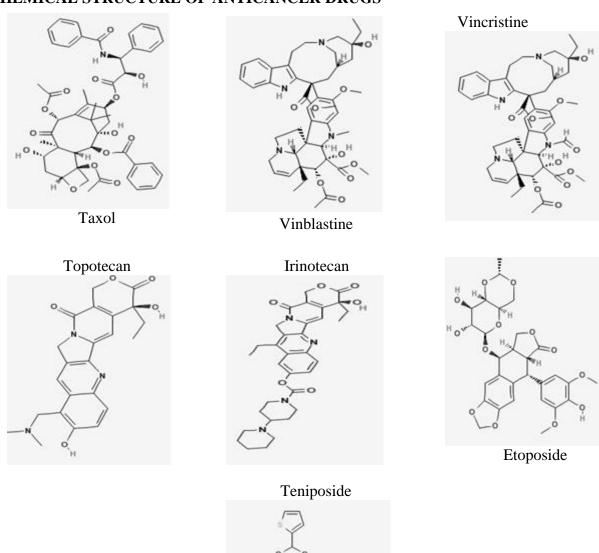
### 6. Etoposide

Belongs to the families of drugs called podophyllotoxin derivatives and topoisomerase inhibitors. Etoposide is a semisynthetic derivative of the podophyllotoxins, an epipodophyllotoxin. It is used in treating various types of cancers including bladder cancer, brain tumours, cervical cancer, ependyoma, germ cell tumor and gestational

trophoblastic neoplasia.

## 7. Teniposide

Belongs to the family of drugs called mitotic inhibitors. Teniposide is a semisynthetic podophyllotoxin derived from the root of *Podophyllum peltatum* (the May apple or mandrake). It is used for treating Acute lymphocytic leukemia and neuroblastoma.

## CHEMICAL STRUCTURE OF ANTICANCER DRUGS

Vincristine

Taxol

Vinblastine

Topotecan

Irinotecan

Etoposide

Teniposide

Biological activity is the result of chemical compound's interaction with biological entity. In clinical study biological entity is represented by human organism. In preclinical testing it is the experimental animals (in vivo) and experimental models (in vitro). Biological activity depends on peculiarities of compound (structure and physico-

chemical properties), biological entity (species, sex, age, etc.), mode of treatment (dose, route, etc.). Any biologically active compound reveals wide spectrum of different effects. Some of them are useful in treatment of definite diseases but the others cause various side and toxic effects. Total complex of activities caused by the compound in biological entities is called the "biological activity spectrum of the substance".Biological activity spectrum of a compound presents every its activity despite of the difference in essential conditions of its experimental determination. The biological activity spectrum of PASS is designed according to the algorithm specified below:

For the compound under prediction structural descriptors are generated. For each activity the following values are calculated:

$$u_j = a_i \, ArcSin\{r_i(2p_{ij}-1)\}, \, u_{0j} = a_i \, ArcSin\{r_i(2p_j-1)\}$$

$$s_j = Sin(u_j/m), \, s_{0j} = Sin(u_{0j}/m)$$

$$Pr_j = (1+(s_j-s_{0j})/(1-s_js_{0j}))/2$$

Then the results are validated and predicted., In case when the probabilities for more than 400 different activities are estimated simultaneously, and the ideal training set should include all referenced biologically active compounds from literature, the best estimate of prediction's quality can be calculated by leave one out cross validation. Each of the compounds is subsequently removed from the training set and the prediction of its activity spectrum is carried out on the basis of the remaining part of the training set. The result is compared to the known activity of a compound, and the maximal error of prediction (MEP) is calculated through the all compounds and activities.

## RESULTS
BIOLOGICAL ACTIVITY SPECTRUM OF THE ANTICANCER DRUGS
*TAXOL*

76 Substructure descriptors; 0 new.

45 Possible activities at Pa > 30%

Pa Pi for Activity:

0,991  0,001   Antimitotic

0,982  0,001   Microtubule formation inhibitor

0,957  0,000   Antimitotic Taxane-like

0,945  0,001   Microtubule formation stimulant

0,850  0,004   Protein-arginine deiminase inhibitor

0,829  0,008   Antineoplastic

0,707  0,006   Antineoplastic enhancer

0,691  0,006   Radiosensitizer

0,652  0,014   CYP2C8 substrate

0,629  0,022   CYP3A substrate

0,661  0,106  Phosphatase inhibitor

0,529  0,001  Beta tubulin antagonist


## *VINBLASTIN*

87 Substructure descriptors; 0 new.

45 Possible activities at Pa > 30%

Pa Pi for Activity:

0,949  0,002  Xenobiotic-transporting ATPase inhibitor

0,931  0,001  Antineoplastic alkaloid

0,912  0,003  Lactose synthase inhibitor

0,896  0,007  Antineoplastic

0,871  0,001  Tubulin antagonist

0,870  0,001  Antineoplastic (multiple myeloma)

0,713  0,027  Teratogen

0,692  0,007  Cytostatic

0,659  0,017  Embryotoxic

0,637  0,029  Toxic

## *VINCRISTINE*

88 Substructure descriptors; 0 new.

31 Possible activities at Pa > 30%

Pa Pi for Activity:

0,941  0,001  Antineoplastic alkaloid

0,917  0,007  Antineoplastic

0,879  0,001  Tubulin antagonist

0,853  0,001  Antineoplastic (multiple myeloma)

0,816  0,003  Leukopoiesis inhibitor

0,802  0,006  Cytostatic

0,742  0,021  Teratogen

0,693  0,014  Embryotoxic

0,675  0,022  Toxic

0,579  0,003  Microtubule formation inhibitor

## *TOPOTECAN*

57 Substructure descriptors; 0 new.

64 Possible activities at Pa > 30%

Pa Pi for Activity:

0,877  0,002  DNA intercalator

0,870 0,002 Topoisomerase I inhibitor

0,875 0,007 Antineoplastic

0,689 0,043 CYP2D16 substrate

0,626 0,010 Antiviral (Influenza)

0,614 0,002 Antineoplastic alkaloid

0,617 0,046 Apoptosis agonist

0,537 0,082 Magnesium protoporphyrin IX monomethyl ester (oxidative) cyclase inhibitor

0,523 0,071 Immunomodulator

0,548 0,107 CYP3A1 substrate

## IRINOTECAN

66 Substructure descriptors; 0 new.

43 Possible activities at Pa > 30%

Pa Pi for Activity:

0,894 0,007 Antineoplastic

0,840 0,002 DNA intercalator

0,810 0,002 Topoisomerase I inhibitor

0,796 0,002 Antineoplastic alkaloid

0,454 0,035 Antiviral (Influenza)

0,437 0,047 Alzheimer's disease treatment

0,533 0,176 Nerve growth factor agonist

0,447 0,112 ®-Pantolactone dehydrogenase (flavin) inhibitor

0,484 0,157 Transplant rejection treatment

0,359 0,034 Tetrahydroxynaphthalene reductase inhibitor

## ETOPOSIDE

61 Substructure descriptors; 0 new.

72 Possible activities at Pa > 30%

Pa Pi for Activity:

0,976 0,005 Hematotoxic

0,930 0,007 Antineoplastic

0,907 0,000 Antimitotic Podophyllotoxin-like

0,819 0,012 Pulmonary hypertension treatment

0,803 0,003 Topoisomerase I inhibitor

0,756 0,006 Carcinogenic, group 2A

0,725 0,008 CYP3A5 substrate

0,696 0,015 Emetic

0,683 0,003 DNA intercalator

0,666   0,002   Antimitotic

*TENIPOSIDE*

67 Substructure descriptors; 0 new.

63 Possible activities at Pa > 30%

Pa Pi for Activity:

0,942   0,006   Antineoplastic

0,902   0,004   Xenobiotic-transporting ATPase inhibitor

0,823   0,010   Cardiotoxic

0,782   0,016   Pulmonary hypertension treatment

0,726   0,004   Topoisomerase I inhibitor

0,717   0,007   Carcinogenic, group 2A

0,657   0,013   CYP2B6 substrate

0,606   0,012   CYP3A5 substrate

0,610   0,017   Beta-amylase inhibitor

0,598   0,027   Emetic

## DISCUSSION

Pa and Pi are the estimates of probability for the compound to be active and inactive respectively for each type of activity from the biological activity spectrum. Their values vary from 0.000 to 1.000. It is reasonably that only those types of activities may be revealed by the compound, which Pa > Pi and so they are put into the biological activity spectrum.

Planning experiments and choosing the activities on which the compound has to be tested, one should have in mind the necessity of balancing between the novelty of pharmacological action and the risk to obtain negative result in experimental testing. Certainly, one will also take into account the particular interest in some kinds of activity, experimental facilities, etc.

The accuracy of prediction is about 90%.

## CONCLUSION

All the seven drugs estimated show a good tendency to fight against the neoplastic cancer, also the drug Irinotecan is against Alzimers disease. Teniposide is not as worthy as others as it is a cardiotoxic. Topotecan, Etaposide and Irinotecan are DNA intercalators. Now a bandwith of drugs for the cancer treatment is analysed, it must be improved and lot of studies have to be continued to ensure its activity invitro and invivo.

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