International Journal of Applied Science & Environmental Engineering – IJASET 2018
Copyright © Institute of Research Engineers and Doctors, SEEK Digital Library
Volume 1 : Issue 1 Publication Date : 28 December, 2018

New fully Metastasis inhibitor drug molecule: 1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin

A new novel drug intended to stop metastatic cancer

Mustafa Pehlivan

***Abstract*— This invention is about the discovery of a new drug molecule that will inhibit the enzyme Tyrosyl DNA Phosphodiesterase 1. TDP1 is a very important enzyme in terms of metastatic cancer treatment as it is involved in repairing damaged DNA of cancer cells. When Cancer cells (tumors) are damaged by Chemotherapeutic anti cancer drugs, tyrosyl DNA Phosphodiesterase 1 is activated and repairs damaged cancer cells. As a result, cancer continues spreading within the body. If Tyrosyl DNA Phosphodiesterase 1 could be stopped doing that, cancer would stop spreading and therefore the cancer Chemotherapy drugs will provide much better therapeutic effects that will lead to stopping cancer. For this reason, targeting Tyrosyl DNA Phosphodiesterase 1 has always been a target for Scientists who work on the discovery of new drug molecules. The purpose of this study is to introduce such a new drug molecule with computational results with the relevant data.**

Keywords— ***anticancer drug, cancer, computation, computational biology, computer modeling, drug discovery, metastasis, tumor metastasis, drug***

Introduction

Tyrosyl DNA Phosphodiesterase 1 is involved in the repairement of cancer as it repairs irreversible top-1 DNA covalent complexes 1. Tyrosyl DNA Phosphodiesterase 1 inhibition can also be beneficial for treating malignant glioma, as identified by Al-Keilani 2 .The aims of this study were to establish a way to computationally predict how this enzyme can be inhibited with a certain novel new drug molecule designed on computer to see what enzymatic activity it may have for specifically and inhibiting only Tyrosyl DNA Phosphodiesterase 1. The online software called "Swiss target predictor'' 3was then used to find such novel molecules, and in one of the trials, such a novel compound that has 95% inhibition efficacy against tyrosyl DNA Phosphodiesterase 1 has been discovered. The molecule was 1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin and figure 1 shows the open formula fort his novel drug molecule along with its inhibition data. The open chemical formula (SMILES) of this molecule was then entered into the ADMET predictor software online to see what Pharmacokinetic effects it may have 4 .The result was that it was a partial inhibitor of glycoproteins which are responsible from clotting 5 .No other potential side effects were shown.
Figure 1 shows the organic structure of the new drug molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin) and Figure 2 shows the enzymatic activity and inhibition efficacy of the new novel drug compound, whereas figure 3 provides ADME (Absorption, Distribution, Metabolism, Elimination) data of this compound.
It is evidenced within this study that a novel effective new drug molecule has been discovered that would treat and cure cancer. In future, it is expected that this drug molecule could be synthesized and then enters clinical trials. It is also expected that this active drug, if successful by the end of clinical trials, should be given to patients suffering from cancer with moderate to high dose vitamin K to prevent inner bleeding as the molecule has potential of inhibiting glycoproteins that may result in thinning blood.

Initial hypothesis
The study was designed by the hypothesis that a molecule that inhibits an enzyme related to cancer resistance mechnanism would be possible.
Electonegative atoms F, Cl, Br and I were known to be used in anticancer therapy when attached on certain Chemical compounds.
As some Brominated compounds as drugs existed previously, the hypothesis was to possibly find a complementary cyclic carbons based new structure with Bromine and Florine groups attahced, but instead of Benzenes, Cyclohexanes which are more active were used.
A new molecule of such has been designed and submitted for in silico computational results and data. The result was amazing as it was a specific and 95% inhibitor of the enzyme mainly responsible from DNA repairment based cancer resistance mechanism, which then causes more tumor growths and eventually metastasis. The targeted enzyme was discovered in 1966 and has been a target with many different Biological ways for stopping metastasis. The enzyme was Tyrosyl DNA Phosphodiesterase 1. Softwares used for the desing of the study were:

- Swiss
- Pass
- AdmetSAR
- MOLinspiration

Claims, synthesis steps strategy and Concluding remarks statements:

1. This invention is a new drug molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin) computationaly predicted to stop cancer from spreading.

2. The drug molecule is shown to highly and specifically inhibit the enzyme Tyrosyl DNA

Phosphodiesterase 1, the enzyme that repairs damaged DNA of cancer cells, according to claim 1.

3. Two figures related to this new drug molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin) have been provided, the former shows the efficacy and enzymatic inhibition levels of the new drug molecule, and the latter shows the Pharmacokinetic ADME (how the drug will be absorbed and work within the body) properties, based on claim 1.

4. This new drug molecule is the first in its own category as there are no other Tyrosyl DNA Phosphodiesterase 1 inhibitors in the market.

5. Once synthesized and clinically tried, this new drug, according to claim 1, will stop metastatis (spreading cancer) and in combination with other anti cancer (Chemotherapy) drug(s), it will provide rapid healing as the damaged DNA of cancer cells will not be repaired anymore, due to the inhibition of the enzyme human Tyrosyl DNA Phosphodiesterase 1. Therefore, synthesis and initiation of clinical trials in relation to this new drug molecule will be highly beneficial in terms of patients suffering from cancer.

6. The synthesis steps for obtaining the molecule, (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin) will be provided here. However, it must be noted that, as the molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin) is not similar to any other known molecule within the Chemical libraries, only generalised synthesis steps will be mentioned as a strategy for obtaining the molecule. These steps will require many transitional steps involving many reactions when the molecule is being synthesized in a Chemistry laboratory, and synthesizing this molecule may take very long time (from months to years). The exact Chemical amounts that should be added in each step and how exactly the molecule will be obtained in detail will need further strategies and discussions by qualified Scientists or Organic Chemists. Generalised Possible Synthesis steps as a strategy for obtaining the molecule is as follows: Obtain liquid Geosmin, a herbal product, otherwise get any kind of sample molecule that has the basic structure of statins. Treat the sample of selection with Lithium Bromide (LiBr) or with Sodium Hydroxide (NaOH) for making a reduction reaction. (This will cause the molecule of selection to remain with a single Methyl group located as attached to certain Carbon atom of two cyclohexanes attached together). Flourounate the product by F2 to get rid of that single methyl group. This will result in obtaining a molecule consisting of two cyclohexanes attached together, where CF3 and F will be attached to a certain carbon atom in the first cyclohexane and where two Flourine (F) atoms will be attached to a certain Carbon atom of the second Cyclohexane. Upon completion of the previous step, add difluorinated Cyclohexane (Cyclohexane that has two Flourine atoms attached on the same Carbon atom) to the mixture. As a final step, fluorinate the resultant molecule as a whole with Flourination reaction, and the final product that will be obtained will be (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin).

Unique Importance of Nano Floro Tricyclohexane (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin):

- Because of the naturally occuring DNA repairment mechanism within the body, there becomes a resistance against cancer treatment. For this reason, Tyrosyl DNA Phosphodiesterase 1 inhibitory molecule(s) has been a target for many years.

- For this reason, Nano Floro Tricyclohexane is a very important drug molecule and is single with such an activity in its category.

- Another importance of this new drug molecule is that it will be used as a complimentary medicine along with Chemotherapy drugs, Radiotherapy and similar other treatments for the purpose of preventing the repair of broken DNA.

- For this reason, this new drug molecule will highly increase the success rate of cancer treatments.

- Another outcome is that the treament duration will be shortened and the quantity and the dosage of anti cancer medicines will be lowered.

- The result this will cause is that the new drug molecule will very much lower the cancer treatment costs spent by the governments and health organizations. Nations and health organizations will therefore show great interest for the drug.

- There are many anticancer medicines used in the present against cancer, but as this drug molecule is single and will be used along with every type of anti cancer medicine(s), it will have a large market value. Because of that, the Pharmaceutical company that will be making this drug product will be the owner of the World market alone. For comparision, today, if a new drug were discovered that will cancel the antibiotic resistance, it would be as important as the discovery of Penicillin. Same way, this new drug molecule which is for cancer treatment has revolutionary importance as it will be cancelling the resistance mechanism of cancer.

- This drug will be a great hope for many cancer patients who are currently on cancer treatment.

Overall advantages of developing the invention as a new novel candidate:

Stopping metastasis by completely inactivating TDP-1 (ie, in non Scientific language, ordering the body to send the cell that has to be repaired into waste.)

Dose reduction and getting rid of bad side effects of Chemoterapy drugs or cancer prevention or cure with a single drug (due to previsiously mentioned "send the cell that has to be repaired into the waste'' mechanism.

Reduction in suffer and Economical costs.

EXPERIMENTAL PROCEDURES

The research has been made by designing a novel compound using free online computational softwares and tools and analyzing its results by reviewing the related previous literature of the same field.

FIGURES

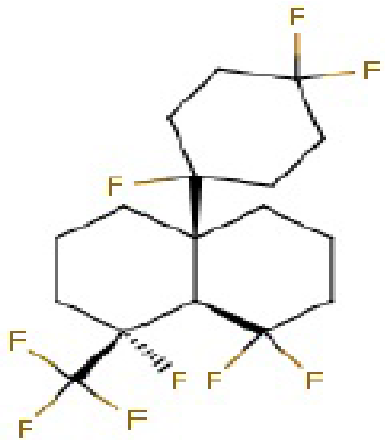

Figure 1: Organic structure of new drug molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin)

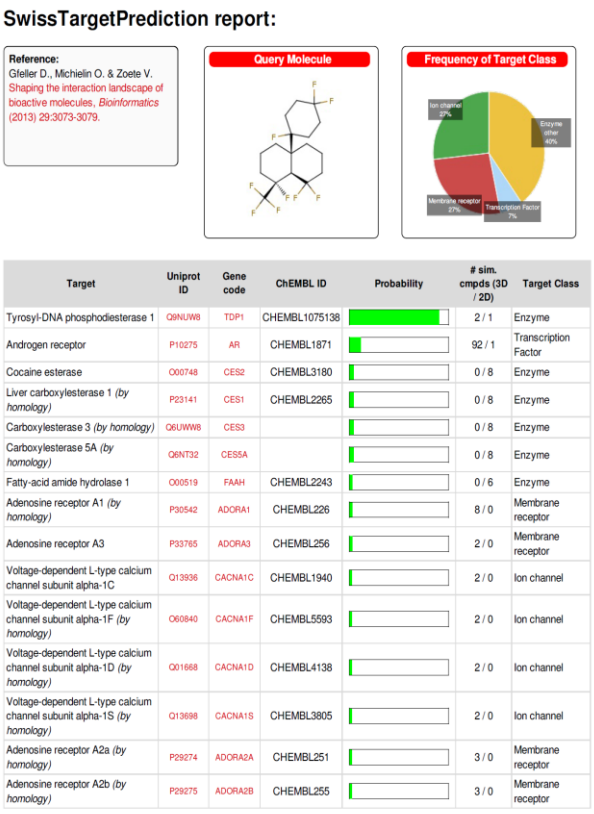

Figure 2: Computationaly Predicted inhibition efficacy of new drug molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin)

Results

ADMET Predicted Profile --- Classification

Model	Result	Probability
Absorption		
Blood-Brain Barrier	BBB+	0.9889
Human Intestinal Absorption	HIA+	1.0000
Caco-2 Permeability	Caco2+	0.6495
P-glycoprotein Substrate	Non-substrate	0.6848

P-glycoprotein Inhibitor	Non-inhibitor	0.7393
	Inhibitor	0.6894
Renal Organic Cation Transporter	Non-inhibitor	0.7955
Distribution		
Metabolism		
CYP450 2C9 Substrate	Non-substrate	0.8667
CYP450 2D6 Substrate	Non-substrate	0.7745
CYP450 3A4 Substrate	Non-substrate	0.6103
CYP450 1A2 Inhibitor	Non-inhibitor	0.6982
CYP450 2C9 Inhibitor	Non-inhibitor	0.7716
CYP450 2D6 Inhibitor	Non-inhibitor	0.9523
CYP450 2C19 Inhibitor	Non-inhibitor	0.8329
CYP450 3A4 Inhibitor	Non-inhibitor	0.9057
CYP Inhibitory Promiscuity	Low CYP Inhibitory Promiscuity	0.6743
Excretion		
Toxicity		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9414
	Non-inhibitor	0.5784
AMES Toxicity	Non AMES toxic	0.8744
Carcinogens	Non-carcinogens	0.7472
Fish Toxicity	High FHMT	0.9841
Tetrahymena Pyriformis Toxicity	High TPT	0.9964
Honey Bee Toxicity	High HBT	0.7510
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.5516
Carcinogenicity (Three-class)	Non-required	0.5282

ADMET Predicted Profile --- Regression

Model	Value	Unit
Absorption		
Aqueous solubility	-4.9013	LogS
Caco-2 Permeability	1.5678	LogPapp, cm/s
Distribution		
Metabolism		
Excretion		
Toxicity		
Rat Acute Toxicity	2.0646	LD50, mol/kg
Fish Toxicity	0.3541	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.8735	pIGC50, ug/L

Figure 3: Computationaly predicted ADME data of new drug molecule (1,8,8-trifluoro, 1 trifluoromethyl, 4a-(1,4,4-trifluorocyclohexyl) decalin)

References

[1] Thomas S. Dexheimer et al. , Tyrosyl DNA Phosphodiesterase as an anticancer therapy, Anticancer Agents Med Chem. 2008 May; 8(4): 381–389

[2] Role of Tyrosyl-DNA Phosphodiesterase I (TDP1) as a Prognostic and Predictiv Factor in Malignant Glioma, Al-Keilani (Iowa Research 2013)

[3] http://www.swisstargetprediction.ch/

[4] http://lmmd.ecust.edu.cn:8000/

[5] Johan W.M. Heemskerk et al., Platelet Activation and Blood Coagulation, Thromb haemost 2002, 88; 186-93

[6] http://www.scbdd.com/mopac-optimization/result/

Countries visited: United Kingdom, Turkey

About Author (s): **MUSTAFA PEHLIVAN**

EDUCATION

High School, Türk Maarif College – 2004-2007

University, University of Hertfordshire, Pharmaceutical Health Science (2015)

Current : Pharmacy (Cyprus International University)

RELATED SKILLS

Language: English

PERSONAL DETAILS

- Date of birth: **June 5, 1990**
- Birthplace: **Nicosia, North Cyprus**
- Marital status: **Single**
- Driver Licence: **North Cyprus**

WORK EXPERIENCE

- Worked in "İyigün Pharmacy'' in Cyprus for two months between the dates 01.06.2014 and 31.07.2014 .

ACTIVITIES\HONORS\ACHIVEMENTS\OTHER

- **"**MERIT'' grade from Personal Transferable Skills 1 (PTS1) module in 2011
- Got 88% from Extemporaneous Manufacturing laboratory exam in the academic year 2013/2014.
- Published a paper entitled "Discovery Of A New Anti Androgen Compound'' in The Journal Of Andrology And Gynecology: Current Research (Scitechnol) in 2015.
- Attenden Dubai Cancer Conference (ICOR 2016; 27-29 October) as a speaker.
- Currently holding an internationally filed drug patent.