Time Minimizing in anticancer drug discovery

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Abstract

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Nowadays, there are plenty of anticancer drugs on the market, and yet there is still an issue in its clinical usage. This is not caused by the absence of anticancer activity, more likely caused by the low bioavailability and high toxicity. Therefore, it motivates researchers to continue the research on effective and safe novel anticancer drug. Synthesis and activity test towards the novel drug are time consuming and costly. In the past, it is even impossible to predict bioavailability, anticancer activity, and toxicity. However, along with the development of new software to predict bioavailability, activity, and toxicity, such issues are becoming more manageable. This approach will ensure benefit in terms of efficiency. It can minimize the amount of trial and error during the process of novel drug candidate selection. Following the use of this software, if the prospective drug compound is predicted to have anti-cancer activity with low bioavailability and high toxicity, further synthesis and activity test in laboratory are no longer needed.

outline

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CADD (Computer Aided Drug Design)
Target Protein Kinases for Cancer Therapy &
Small molecule inhibitors
Trials design to evaluate targeted agents
Closing

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Introduction

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The field of anticancer therapeutics is at a critical point in its development.

http://www.who.int/news-room/fact-sheets/detail/cancer

1 February 2018

Key facts

1. Cancer is the second leading cause of death globally, and was responsible for 8.8 million deaths in 2015.
2. Globally, nearly 1 in 6 deaths is due to cancer.
3. Approximately 70% of deaths from cancer occur in low- and middle-income countries.
4. Around one third of deaths from cancer are due to the 5 leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol use.
5. Tobacco use is the most important risk factor for cancer and is responsible for approximately 22% of cancer deaths (2).

6. Cancer causing infections, such as hepatitis and human papilloma virus (HPV), are responsible for up to 25% of cancer cases in low- and middle-income countries (3).
7. Late-stage presentation and inaccessible diagnosis and treatment are common. In 2017, only 26% of low-income countries reported having pathology services generally available in the public sector. More than 90% of high-income countries reported treatment services are available compared to less than 30% of low-income countries.
8. The economic impact of cancer is significant and is increasing. The total annual economic cost of cancer in 2010 was estimated at approximately US$ 1.16 trillion (4).
9. Only 1 in 5 low- and middle-income countries have the necessary data to drive cancer policy (5).

Cancer is a leading cause of death worldwide, accounting for 8.8 million deaths in 2015.

The most common causes of cancer death are cancers of:

- Lung (1.69 million deaths)
- Liver (788 000 deaths)
- Colorectal (774 000 deaths)
- Stomach (754 000 deaths)
- Breast (571 000 deaths)

Anticancer drug discovery has continued to be a very interesting field of research, but synthesis and activity test towards the novel drug are time consuming and costly.

Drug discovery steps:

1. Drug Design,
2. Synthesis and
3. Evaluation of New Anticancer Drugs

Many drugs still fail in cancer patient therapy even after advanced clinical trials and safety testing, why?

The answer is usually a result of an unfavorable absorption, distribution, metabolism, and excretion/toxicity (ADME/T) profile.

In the past, it was difficult to almost impossible to predict these characteristics for a specific compound. Drug discovery in the new millennium is armed with not only new and efficient techniques for producing, purifying and screening new entities, but with computing power that was unimaginable a decade ago. Hence, with data compiled from other commercial agents, we can *a priori* predict ADME/T properties of lead molecules *in silico*

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CADD (Computer Aided Drug Design)

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Drug discovery steps become:

1.Computer Aided Drug Design,

2.Synthesis and

3.Evaluation of NewAnticancer Drugs

***IN SILICO* ADME-TOX STUDY**

Ex. CDI-lab, pkCSM, The Pentium IV work station and Pallas 6.1.1 software were used to calculate and to predict the ADMET properties of the molecules.
Chem draw ultra software was used to draw the structure of the compounds to be analyzed and was saved as MDL file. The sketched molecules were undergo calculation of the following properties viz drug likeliness, metabolite, toxicity, etc.

***IN SILICO* ACTIVITY TEST BY MOLECULAR DOCKING only involve electronic and steric properties.**

Ex. MVD 5.0, Autodoc, MOE, Maestro, etc.

It needs to check lipophylic property. The predicted drug likeliness of the compounds follow the Lipinski "Rule of Five" that all four parameter values for a compound are less than five for log P and H-bond donors and multiples of five for H-bond acceptors and molecular weight showed that the compounds might have good absorption/ or permeability properties.

THREE-DIMENSIONAL PHARMACOPHORE MAPPING

The 3D pharmacophore search is an important, robust and a facile approach to rapidly identify lead compounds against a desired target. Traditionally, a pharmacophore is defined as the specific 3D arrangement of functional groups within a molecular framework that are necessary to bind to a macromolecule and/or an enzyme active site. The designation of a pharmacophore is the first essential step towards understanding the interaction between a receptor and a ligand. Once a pharmacophore is established, the medicinal chemist has a host of 3D database search tools to retrieve novel compounds that fit the pharmacophore model. The search algorithms have evolved over the years to effectively identify and optimize leads, focus combinatorial libraries and assist in virtual high-throughput screening. Thus, this technology has been clearly established as one of the successful computational tools in modern drug design

HIGH-THROUGHPUT DOCKING

Docking is simply active or a designated site of a protein and referred to the ability to position a ligand in the calculate specific binding affinities. Ligand-protein docking has evolved so remarkably throughout the past decade that docking single or multiple small molecules to a receptor site is now routinely used to identify ligands. Optimal docking procedures need to be fast, generate reliable ligand geometries, rank the ligand conformation correctly (scoring), and thereby, estimate the binding energy. A number of studies have shown that docking algorithms are capable of finding ligands and binding conformations at a receptor site close to experimentally determined structures (see below). These algorithms are equally applicable to the identification of multiple proteins to which a small molecule can bind. The application of this approach may facilitate the prediction of either unknown and secondary therapeutic target proteins or side effects and toxicity of particular drugs

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Target Protein Kinases for Cancer & Small molecule inhibitors

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The large number of validated targets and new drugs have been developed. Modern anticancer drug research has become increasingly focused on targeted drug therapy, and many of the validated targets are transduction-related macromolecules. In the 1980s, protein kinases were first shown to have an important role in oncogenesis and tumor progression, and since then they have received increasing attention as targets for anticancer drugs. Several kinase inhibitors are now approved for the treatment of cancer, and many more are advancing through clinical trials.

Protein kinases (PTKs) are enzymes that regulate the biological activity of proteins by phosphorylation of specific amino acids with ATP as the source of phosphate, thereby inducing a conformational change from an inactive to an active form of the protein

Most PTKs are related to oncogenes, and approximately 16 of them are considered as possible therapeutic targets. Based on their localization and structure, these enzymes are classified as receptor- or non-receptor PTKs. Receptor protein kinases (RPTKs) have dual roles: as receptors and as enzymes.
They have a hydrophobic domain that transverses the cell membrane, an extracellular ligand-binding
domain that recognizes an external messenger (growth hormones or growth factors), and a cytoplasmatic kinase domain that becomes activated upon binding of the external messenger, triggering a signaling cascade that ultimately controls the transcription of specific genes related to cellular proliferation and differentiation.

Non-receptor PTKs are activated by upstream signaling molecules such as G protein-coupled receptors, immune system receptors, or RPTKs. They have no transmembrane or extracellular domains and are not covalently bound to a membrane receptor, nor anchored to the phospholipid membrane via a lipid modification.

Ligand binding to a RPTK induces its dimerization or oligomerization, leading to interactions between adjacent cytoplasmic domains with accompanying activation of the kinase moiety. Activation of a non-receptor kinase is similarly induced in response to the appropriate extracellular signal, but dimerization may or may not be necessary for activation. The activated kinase then initiates a cascade of phosphorylation reactions resulting in the activation of other proteins, as well as the production of secondary messengers that transmit the signal to the nucleus.

All protein kinases have a region in their active site that recognizes ATP, which is the phosphorylating

agent in all cases, as well as another region for their substrates. Most clinically used inhibitors interact with these ATP recognition sites that, despite having a common substrate, are relatively different for different kinases, making possible some selectivity in the inhibition. Very often, structurally close compounds bind to the ATP site in different topologies and are able to recognize different kinases. For this reason, chemical similarity between kinase inhibitors often fails to correlate with target specificity.

Binding to an adjacent allosteric site or to an inactive form of the kinase has also been exploited.

In *Targeting Protein Kinases for Cancer Therapy*, the drugs that inhibit them are called small molecule inhibitors. Compounds (usually a small organic molecule) demonstrate a desired biological activity on a validated molecular target.

Some of Selected Kinase Inhibitors in the Market or That Have Entered Clinical Development

Type	Target	Agents
Tyr kinases	EGFR (HER-1)	Small-molecule inhibitors Gefitinib (ZD-1839, Iressa®) Erlotinib (OSI-774, Tarceva®) Lapatinib (GW-2016, Tyverb®) Canertinib (CI-1033) Afatinib (BIBW-2992, Gilotrif®) EKI-785 Pelitinib (EKB-569) Neratinib (HKI-272) AZD-9291 CO-1686

Type	Target	Agents
		Monoclonal antibodies Cetuximab (IMC-C225, Erbitux®) Panitumumab (ABX-EGF, Vectibix®) Matuzumab (EMD-72000) Nimotuzumab MDX-447
	HER-2 (ErbB2)	Small-molecule inhibitor ARRY-380 (ONT-380) Monoclonal antibodies Trastuzumab (Herceptin®) Pertuzumab (2C4, Perjeta®)
	HER-3	Monoclonal antibodies MM-121 U3-1287 LJM716
	Pan-HER	Small-molecule inhibitor Varlitinib (ARRY-543, ASLAN001)
	IGF-1R	Small-molecule inhibitors AEW-541 INSM-18 (nordihydroguaiaretic acid, NDGA) BVP-51004 (cyclolignan PPP)

		Antibodies Figitumumab (CP-751871) Ganitumab (AMG-479)
	HGFR (c-Met)	Small-molecule inhibitors Tivantinib (ARQ 197) JNJ-38877605 PF-04217903 NC280 (INCB-28060)
	VEGF, VEGFR, and related receptors	Small-molecule inhibitors Semaxanib (SU-5416) SU-6668 Sunitinib (SU-11248, Stutent®) Vatalanib (PTK-787, ZK-222584) Cediranib (AZD-2171, Recentin®) Foretinib (EXEL-2880, GSK-1363089, XL-880) Cabozantinib (Cometriq®, XL184) Tivozanib (AV-951) Lenvatinib (E-7080, Lenvima®) Linifanib (ABT-869) Pazopanib (GW-786034, Votrient®) Axitinib (AG-013736, Inlyta®) Nintedanib (BIBF1120, Vargatef®) CEP-5214

	CEP-7055
	Monoclonal antibody
	Bevacizumab (Avastin®)
	Soluble decoy receptor
	Ziv-aflibercept (Zaltrap®)
	Ribozyme
	Angiozyme (RPI.4610)
PDGFRs	Small-molecule inhibitor
	Suramin (Metaret®)
FGFRs	Small-molecule inhibitors
	Dovitinib (TKI258)
	BGJ398 (NVP-BGJ398)
	Monoclonal antibody
	PRO-001
FLT3 (CD135)	Small-molecule inhibitors
	Tandutinib (MLN-518, CT-53518)
	Lestaurtinib (CEP-701)
	Midostaurin (PKC-412)
Bcr-Abl	Small-molecule inhibitors
	ATP mimics
	Imatinib (STI-571, Glivec®)
	Nilotinib (AMN-107, Tasigna®)
	Radotinib (Supect®)
	Ponatinib (AP24534, Iclusig®)
	Tyrosine mimics
	Adaphostin (NSC-680410)
	ON-012380

Trials design to evaluate targeted agents

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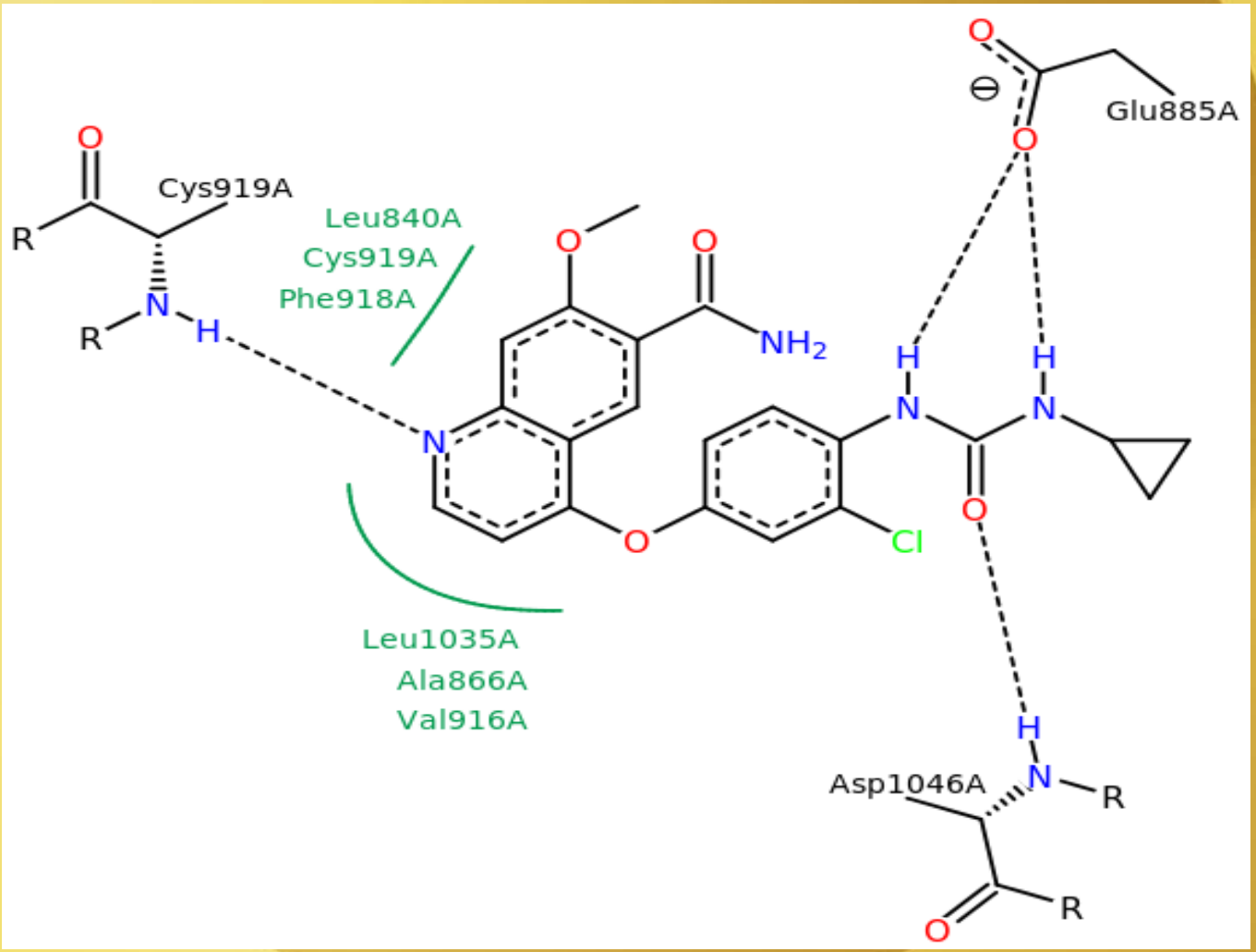
LEAD OPTIMIZATION

Starting with the prospective lead compound to structural modification in order to develope structure-activity relationship (SAR) and quantitative SAR (QSAR) one can gain tremendous information. These approaches have been modified remarkably and the researcher now has a plethora of resources under his/her disposal before the actual synthesis begins.

Lenvatinib
(thyroid cancer &
renal cell carcinoma)

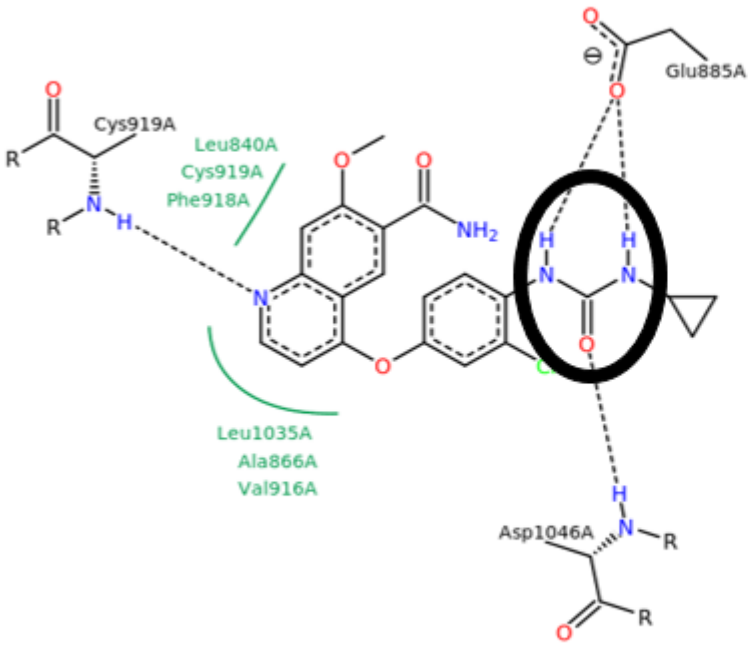
Multiple Tyrosine Kinase Inhibitor

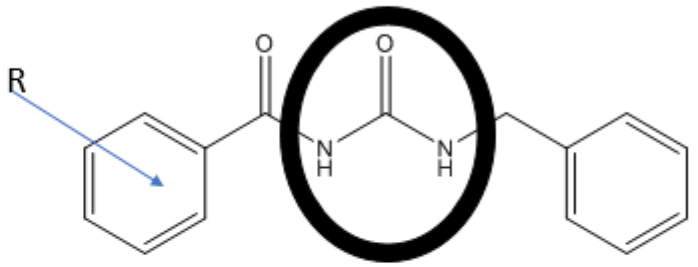


On February 13, 2015, lenvatinib (Lenvima; Eisai),
An oral, multireceptor tyrosine kinase inhibitor, was approved by the US Food and Drug Administration (FDA)
to treat patients with locally recurrent or metastatic, progressive, radioactive iodine–refractory differentiated thyroid cancer.

FDA approves lenvatinib for unresectable hepatocellular carcinoma [news release]. Silver Spring, MD; August 16, 2018: FDA website. http://www.pharmacytimes.com/link/206.

Accessed August 16, 2018.

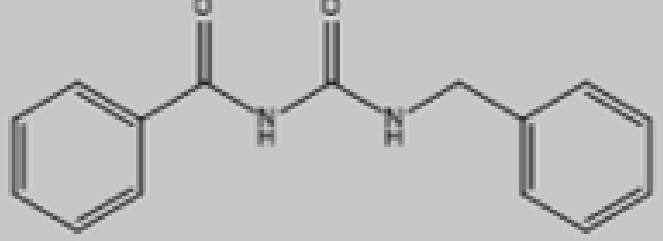
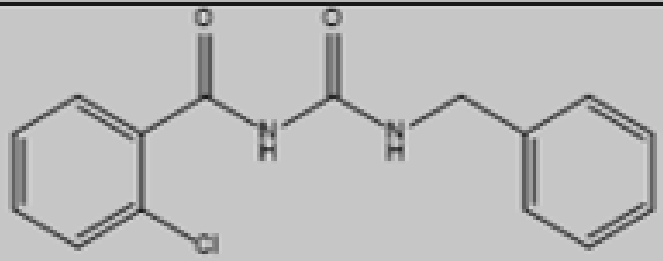
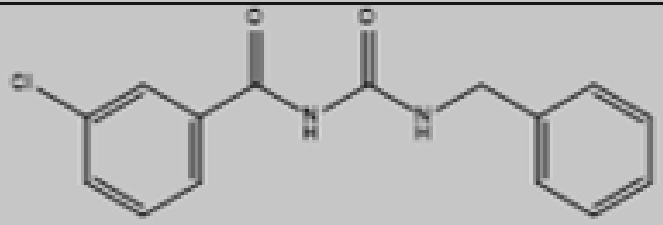
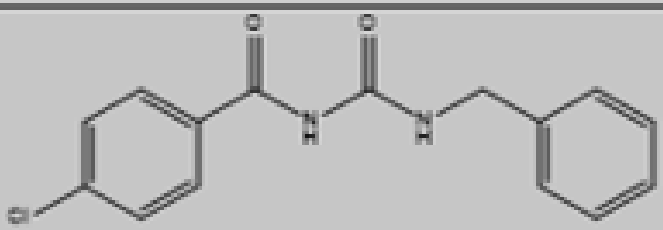


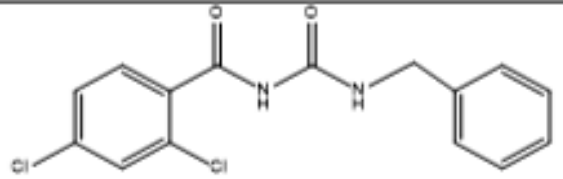
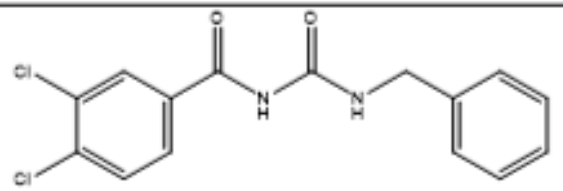
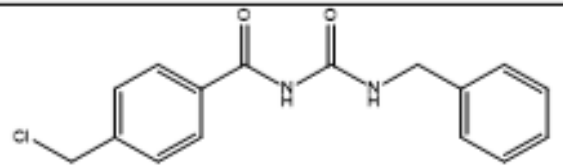
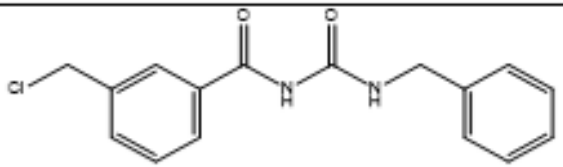
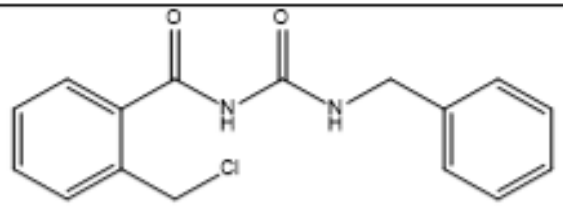
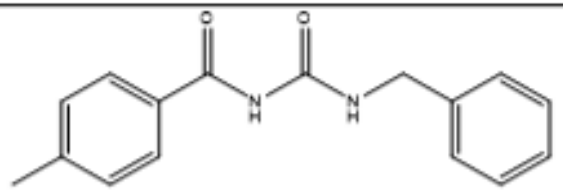
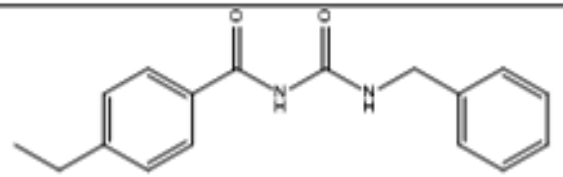


1-BENZYL-3-BENZOYLUREA AND ANALOGS

Structural modification of 1-benzyl-3-benzoylurea lead compound by inserting 22 lipophilic and electronic groups into benzoyl group in order to increase activity

The same pharmacophore compare to Lenvatinib is the reason to do molecular docking all test compound as VEGFR-2 inhibitor(PDB code: 3WZD)

1.	*1-benzyl-3-benzoylurea*	
2.	*1-benzyl-3-(2-chloroo)-benzoylurea*	
3.	*1-benzyl-3-(3- chloro)-benzoylurea*	
4.	*1-benzyl-3-(4-chloro)-benzoylurea*	

5.	*1-benzyl-3-(2,4-dichloro)-benzoylurea*	
6.	*1-benzyl-3-(3,4-dichloro)-benzoylurea*	
7.	*1-benzyl-3-(4-chloromethyl)-benzoylurea*	
8.	*1-benzyl-3-(3-chloromethyl)-benzoylurea*	
9.	*1-benzyl-3-(2- chloromethyl)-benzoylurea*	
10.	*1-benzyl-3-(4-methyl)-benzoylurea*	
11.	*1-benzyl-3-(4-ethyl)-benzoylurea*	

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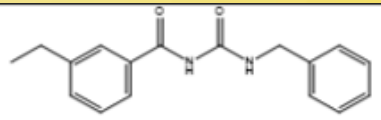
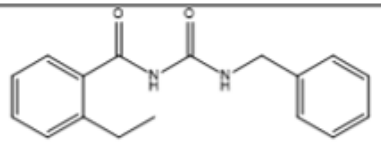
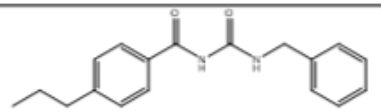
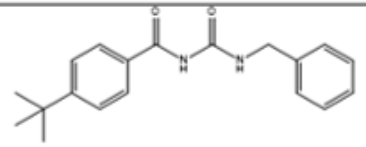
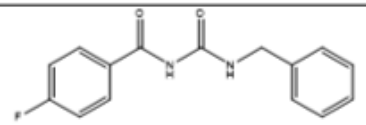
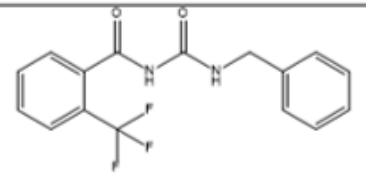
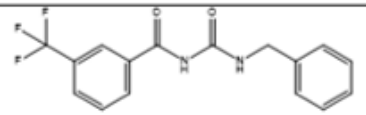
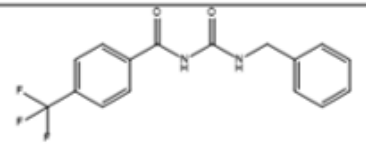
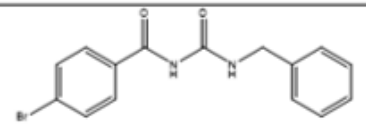
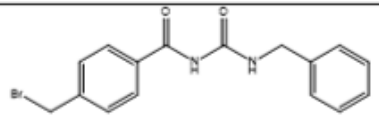
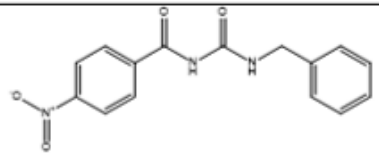
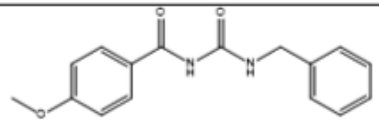
12.	*1-benzyl-3-(3-ethyl)-benzoylurea*	
13.	*1-benzyl-3-(2-ethyl)-benzoylurea*	
14.	*1-benzyl-3-(4-propyl)-benzoylurea*	

15.	*1-benzyl-3-(4-t-butyl)-benzoylurea*	
16.	*1-benzyl-3-(4-fluoro)-benzoylurea*	
17.	*1-benzyl-3-(2-trifluoromethyl)-benzoylurea*	
18.	*1-benzyl-3-(3-trifluoromethyl)-benzoylurea*	
19.	*1-benzyl-3-(4-trifluoromethyl)-benzoylurea*	
20.	*1-benzyl-3-(4-bromo)-benzoylurea*	

21.	*1-benzyl-3-(4- bromomethyl)-benzoylurea*	
22.	*1-benzyl-3-(4- nitro)-benzoylurea*	
23.	*1-benzyl-3-(4- methoxy)-benzoylurea*	

Lipinski “Rule of five”result

No	Compound	Mr (g/mol)	LogP	H Donor	H Aseptor
1	*1-benzyl-3-benzoylurea*	254.28	2.53	2	2
2	*1-benzyl-3-(2-chloroo)-benzoylurea*	288.73	3.09	2	2
3	*1-benzyl-3-(3- chloro)-benzoylurea*	288.73	3.09	2	2
4	*1-benzyl-3-(4-chloro)-benzoylurea*	288.73	3.09	2	2
5	*1-benzyl-3-(2,4-dichloro)-benzoylurea*	323.17	3.65	2	2
6	*1-benzyl-3-(3,4-dichloro)-benzoylurea*	323.17	3.65	2	2

7	*1-benzyl-3-(4-chloromethyl)-benzoylurea*	302.76	3.18	2	2
8	*1-benzyl-3-(3-chloromethyl)-benzoylurea*	302.76	3.18	2	2
9	*1-benzyl-3-(2-chloromethyl)-benzoylurea*	302.76	3.18	2	2
10	*1-benzyl-3-(4-methyl)-benzoylurea*	268.31	3.023	2	2
11	*1-benzyl-3-(4-ethyl)-benzoylurea*	282.34	3.43	2	2
12	*1-benzyl-3-(3-ethyl)-benzoylurea*	282.34	3.43	2	2
13	*1-benzyl-3-(2-ethyl)-benzoylurea*	282.34	3.43	2	2
14	*1-benzyl-3-(4-propyl)-benzoylurea*	296.36	3.85	2	2
15	*1-benzyl-3-(4-t-butyl)-benzoylurea*	310.39	4.23	2	2

16	*1-benzyl-3-(4-fluoro)-benzoylurea*	272.27	2.69	2	2
17	*1-benzyl-3-(2-trifluoromethyl)-benzoylurea*	322.28	3.45	2	2
18	*1-benzyl-3-(3-trifluoromethyl)-benzoylurea*	322.28	3.45	2	2
19	*1-benzyl-3-(4-trifluoromethyl)-benzoylurea*	322.28	3.45	2	2
20	*1-benzyl-3-(4-bromo)-benzoylurea*	333.18	3.36	2	2
21	*1-benzyl-3-(4-bromomethyl)- benzoylurea*	347.21	3.3	2	2
22	*1-benzyl-3-(4- nitro)-benzoylurea*	299.28	1.94	2	4
23	*1-benzyl-3-(4- methoxy)-benzoylurea*	284.31	2.4	2	3
	Hydroxyurea	76.05	-1.12	3	2
	5-fluorouracil	130.08	-0.9	2	2
	Lenvatinib	426.85	2.1	3	5

Prediction % absorbtion using pkCSM

No.	Compound	% abs > 30%)
1	*1-benzyl-3-benzoylurea*	91.797
2	*1-benzyl-3-(2-chloroo)-benzoylurea*	90.109
3	*1-benzyl-3-(3- chloro)-benzoylurea*	91.054
4	*1-benzyl-3-(4-chloro)-benzoylurea*	90.416
5	*1-benzyl-3-(2,4-dichloro)-benzoylurea*	88.727
6	*1-benzyl-3-(3,4-dichloro)-benzoylurea*	90.131
7	*1-benzyl-3-(4-chloromethyl)-benzoylurea*	90.732
8	*1-benzyl-3-(3-chloromethyl)-benzoylurea*	90.694
9	*1-benzyl-3-(2- chloromethyl)-benzoylurea*	89.123
10	*1-benzyl-3-(4-methyl)-benzoylurea*	91.874
11	*1-benzyl-3-(4-ethyl)-benzoylurea*	91.806

12	*1-benzyl-3-(3-ethyl)-benzoylurea*	91.768
13	*1-benzyl-3-(2-ethyl)-benzoylurea*	90.197
14	*1-benzyl-3-(4-propyl)- benzoylurea*	91.034
15	*1-benzyl-3-(4-t-butyl)- benzoylurea*	90.262
16	*1-benzyl-3-(4-fluoro)-benzoylurea*	91.317
17	*1-benzyl-3-(2-trifluoromethyl)-benzoylurea*	88.497
18	*1-benzyl-3-(3-trifluoromethyl)-benzoylurea*	89.541
19	*1-benzyl-3-(4-trifluoromethyl)-benzoylurea*	89.505
20	*1-benzyl-3-(4-bromo)-benzoylurea*	90.349
21	*1-benzyl-3-(4- bromomethyl)-benzoylurea*	90.557
22	*1-benzyl-3-(4- nitro)-benzoylurea*	82.368
23	*1-benzyl-3-(4- methoxy)-benzoylurea*	92.773
	Hydroxyurea	73.704
	5-fluorouracil	87.223
	Lenvatinib	84.799

Prediction in-silico activity using Molegro Virtual Docker 5.0

RMSD = 0,646062

No.	Compound	*Rerank Score(kcal/mol)*
1	*1-benzyl-3-benzoylurea*	-90.3715
2	*1-benzyl-3-(2-chloroo)-benzoylurea*	-91.2155
3	*1-benzyl-3-(3- chloro)-benzoylurea*	-87.166
4	*1-benzyl-3-(4-chloro)-benzoylurea*	-85.6658
5	*1-benzyl-3-(2,4-dichloro)-benzoylurea*	-83.9519
6	*1-benzyl-3-(3,4-dichloro)-benzoylurea*	-81.8889
7	*1-benzyl-3-(4-chloromethyl)-benzoylurea*	-82.1469
8	*1-benzyl-3-(3-chloromethyl)-benzoylurea*	-86.0169

9	*1-benzyl-3-(2- chloromethyl)-benzoylurea*	-86.5096
10	*1-benzyl-3-(4-methyl)-benzoylurea*	-81.9729
11	*1-benzyl-3-(4-ethyl)-benzoylurea*	-82.5089
12	*1-benzyl-3-(3-ethyl)-benzoylurea*	-83.5294
13	*1-benzyl-3-(2-ethyl)-benzoylurea*	-91.5842
14	*1-benzyl-3-(4-propyl)- benzoylurea*	-88.1971
15	*1-benzyl-3-(4-t-butyl)- benzoylurea*	-80.853
16	*1-benzyl-3-(4-fluoro)-benzoylurea*	-89.4971
17	*1-benzyl-3-(2-trifluoromethyl)-benzoylurea*	-86.5934
18	*1-benzyl-3-(3-trifluoromethyl)-benzoylurea*	-87.4362
19	*1-benzyl-3-(4-trifluoromethyl)-benzoylurea*	-82.601
20	*1-benzyl-3-(4-bromo)-benzoylurea*	-82.5543
21	*1-benzyl-3-(4- bromomethyl)-benzoylurea*	-81.4373
22	*1-benzyl-3-(4- nitro)-benzoylurea*	-88.6502
23	*1-benzyl-3-(4- methoxy)-benzoylurea*	-84.0985
	Hydroxyurea	-44.5302
	5-fluorouracil	-52.6336
	Lenvatinib	-124.545

ProTox-Predicition of Rodent Oral Toxicity

No.	Compound	Toxicity Parameter LD-50 (mg/kg)
1	*1-benzyl-3-benzoylurea*	1950
2	*1-benzyl-3-(2-chloroo)-benzoylurea*	3000
3	*1-benzyl-3-(3- chloro)-benzoylurea*	2000
4	*1-benzyl-3-(4-chloro)-benzoylurea*	2000
5	*1-benzyl-3-(2,4-dichloro)-benzoylurea*	2000
6	*1-benzyl-3-(3,4-dichloro)-benzoylurea*	2000
7	*1-benzyl-3-(4-chloromethyl)-benzoylurea*	1950
8	*1-benzyl-3-(3-chloromethyl)-benzoylurea*	3000
9	*1-benzyl-3-(2- chloromethyl)-benzoylurea*	3000
10	*1-benzyl-3-(4-methyl)-benzoylurea*	818
11	*1-benzyl-3-(4-ethyl)-benzoylurea*	2000
12	*1-benzyl-3-(3-ethyl)-benzoylurea*	2000
13	*1-benzyl-3-(2-ethyl)-benzoylurea*	2000
14	*1-benzyl-3-(4-propyl)- benzoylurea*	2000
15	*1-benzyl-3-(4-t-butyl)- benzoylurea*	2000
16	*1-benzyl-3-(4-fluoro)-benzoylurea*	2000
17	*1-benzyl-3-(2-trifluoromethyl)-benzoylurea*	3000
18	*1-benzyl-3-(3-trifluoromethyl)-benzoylurea*	2000
19	*1-benzyl-3-(4-trifluoromethyl)-benzoylurea*	818

20	*1-benzyl-3-(4-bromo)-benzoylurea*	2000
21	*1-benzyl-3-(4- bromomethyl)-benzoylurea*	1950
22	*1-benzyl-3-(4- nitro)-benzoylurea*	2850
23	*1-benzyl-3-(4- methoxy)-benzoylurea*	2000
	Hydroxyurea	5760
	5-fluorouracil	115
	Lenvatinib	3000

General result

COMPOUND	Lipinski "Rule of five"result	% Abs. prediction result	In silico activity prediction result (RS , kkcal/mol)	Toxicity prediction result (LD50, mg/kg)
All	Meet the requirement	82.368- 92.733	-81,4173 – -91,5842	818-3000
Lenvatinib	Meet the requirement	84.799	-124,545	3000

What are your recommendation???

Some of test compounds are recommended to further synthesize and advance activity test

CLOSING

Computer-Aided Drug Design (CADD) or Structure-Based Drug Design (SBDD) has made a time minimizing to the field of novel anticancer drug discovery

http://www.who.int/news-room/fact-sheets/detail/cancer

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