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ViridisChem's Chemical Analyzer during drug-discovery

Goal of the case-study

This case-study will show how the ViridisChem's Chemical Analyzer can be used to get full (predicted) toxicity profiles of potential drug targets and their analogs or metabolites, so that high risk drug targets can be identified even before the R&D efforts start, allowing scientists to focus on less toxic analogs/metabolites. By utilizing this powerful capability, companies can build a very focused drug target list, avoid wasted R&D effort (that would have been spent on high-risk drug targets that later get eliminated), and save many weeks of valuable R&D efforts by having the information about the molecules available within seconds.

Understanding the toxicity of all the analogs and metabolites of a known drug molecule also provides interesting insights to scientists who are looking to re-purpose a drug or to find generic applications for that drug. For this case-study, we have chosen a well-known drug molecule, Thalidomide and its analogs, to illustrate the product use.

Company Background

ViridisChem has built one of the largest, highly curated toxicity databases with 93 million chemicals and 48 physical and toxicological properties per chemical. Each chemical is tagged extensively with functional classifications, as well as physical and chemical characteristics that help to identify its reactivity towards other chemicals, and its toxicity potential. ViridisChem has developed an AI powered software platform that enables real-time execution of over 150 industry standard prediction models that predict various physical and toxicological properties of new/postulated chemicals (small, large molecules, proteins, etc.). ViridisChem serves as the provisioning platform for toxicity information of every chemical and offers real-time execution access to most industry-standard prediction models. Given a molecule, the platform can also identify most of the analogs and metabolites of the molecule and offer toxicity evaluation of these analogs or metabolites.

The product Chemical Analyzer by ViridisChem offers an in-depth analysis of ecological, health, and safety-related toxicity scores using internal algorithms based on the physical and toxicological properties. Score algorithms are defined using OECD (Organization for Economic Co-operation and Development), United Nations and US-OSHA GHS (Globally Harmonized System) Guidelines. The scores are depicted visually through easy-to-understand spider graph and are calibrated from 0 to 4; where 0 = None (or unknown) toxicity; 1, 2, 3 = increasingly higher toxicity; and 4 = Extreme toxicity. The area outlined by color-coded lines is indicative of the toxicity of the molecule (larger the area, more toxic the molecule).

While comparing multiple chemicals and their toxicity, the spider graph shows the color-coded areas indicative of each chemical's toxicity overlaid on top of each other to visually illustrate the differentiation.

Some of the health risk predictions the Chemical analyzer provides are:

Chronic Health: Carcinogenicity, Genotoxicity, Mutagenicity, Reproductive toxicity, Neurotoxicity, Endocrine disruption, organ toxicity (in liver, GI track, etc.)
Acute Health**:** Skin corrosion/irritation, Eye irritation, Inhalation toxicity, Oral toxicity, Skin sensitization
Safety: Flammability, radioactivity, explosivity, water reactivity

Where possible, the toxicological properties include LC50, LD50, EC50 values for various species to help understand the acute and chronic health impact of the chemicals.

All of these capabilities combined can offer various R&D insights during drug target identification that otherwise are not possible. By integrating the Chemical analyzer as part of its R&D practices, pharmaceutical and agrochemical companies can automate this exploratory work to identify high-risk drug targets, find less toxic analogs or metabolites to save precious R&D time and efforts.

Study Approach

To illustrate the use of the platform and the product, we have selected a well-known and well-studied drug molecule Thalidomide (CAS# 50-35-1) as an example for this case study.

History behind the target molecule

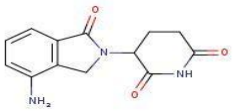
Thalidomide was synthesized in 1953 by a West German company as a sedative. It became popular outside of the United States to help with morning sickness in the mid-1950s, but in 1961 it was discovered to cause birth defects. But despite these widespread reproductive issues associated with thalidomide, it continues to be used in medical settings due to its usefulness in the treatment of a number of conditions and diseases, and Thalidomide and its derivatives[1] are now widely used as potent immunomodulatory drugs (IMiDs) in the treatment of several diseases including multiple myeloma (MM) and leprosy. We have selected this molecule for our case-study as an illustrative example because it is one of the most widely studied molecules and lot of information is available about its many analogs and metabolites.

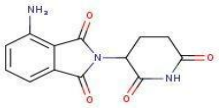
Please note that the purpose of this case-study is not to provide any recommendation on suitability of specific molecules, but simply to show what type of information can be available for early drug-discovery studies that can save precious R&D time, especially for molecules for which very little information is available.

We have selected following analogs and metabolites of the molecule:

Analogs:

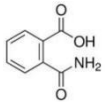
- Lenalidomide (CAS# 191732-72-6)
- Pomalidomide (CAS# 19171-19-8)

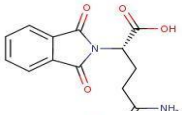


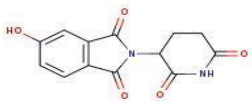


Metabolites:

- Phthalamic acid (CAS# 88-97-1)
- N-Phthaloylglutamine (CAS# 3343-29-1)
- 5-Hydroxythalidomide (CAS# 64567-60-8)







For this case-study, we have focused on two of the ViridisChem Platform's key capabilities:

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- Given a (new or unknown) molecular structure, identify the appropriate prediction models that will offer the highest accuracy property predictions and execute them in real time in the background to estimate physical and toxicological properties, acute and chronic health concerns.

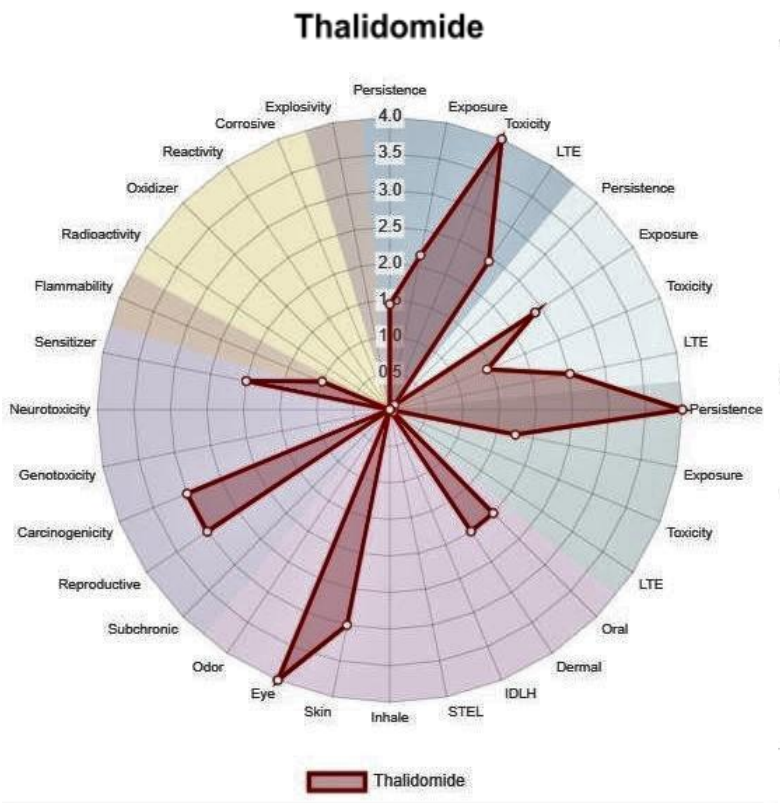
- Based on the property values (experimental or estimated), utilize ViridisChem's proprietary algorithms to calculate toxicity scores. Sort the results according to the toxicity scores

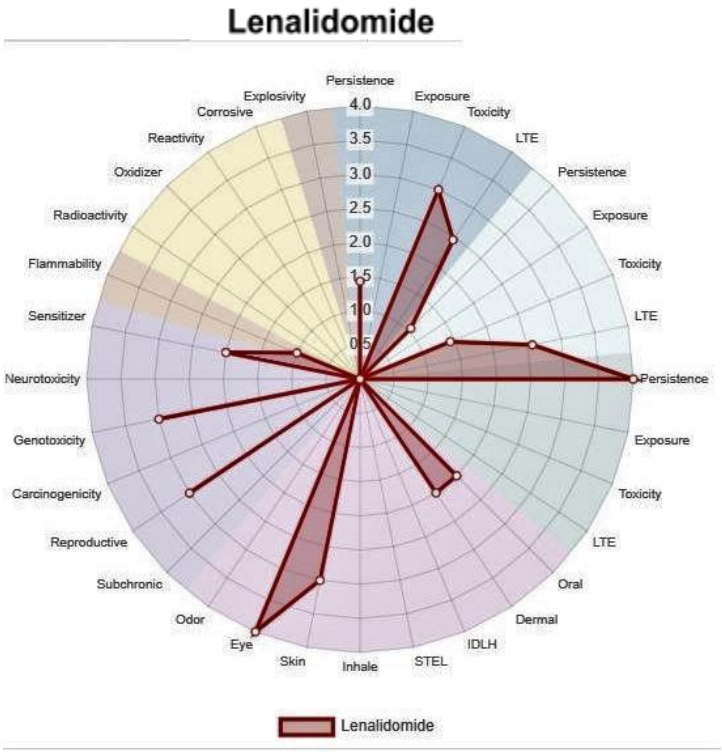
Combining these capabilities, ViridisChem's Chemical analyzer was able to identify the Thalidomide analogs and metabolites and compare their toxicities, so that scientists can identify if the target molecule is high-risk and if they should pursue its analog or metabolite. Of course, this is a preliminary information to help scientists quickly assess potential problems and factor that information during their target identification work.

Two of the key capabilities critical during drug-discovery R&D this case-study does not focus on (since we have already selected the analogs and metabolites we want to focus on) are:

- Its ability to identify the analogs and metabolites of a given molecule along with their toxicity profiles
- When the scientist draws a structure of a new/unknown or even postulated molecules, its ability to select and execute on-demand appropriate prediction models to provide most physical and toxicological properties and the molecule's toxicity profile

For the molecule Thalidomide, from the visual toxicity evaluation graphs generated using ViridisChem's Chemical analyzer (see below), each molecule has different health and ecological toxicity footprint. Scientists must take into consideration their specific application requirements (therapeutic target, mode of delivery, etc.) that can influence their decision.





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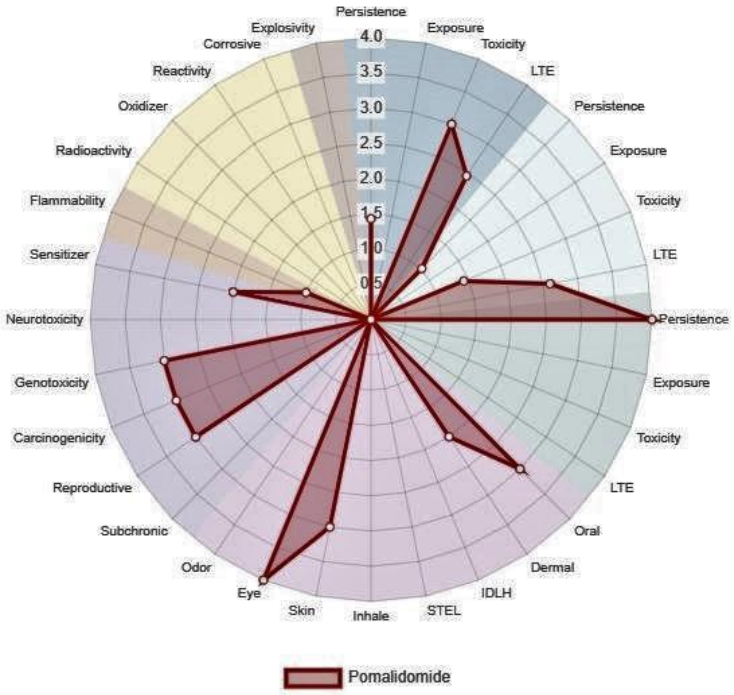
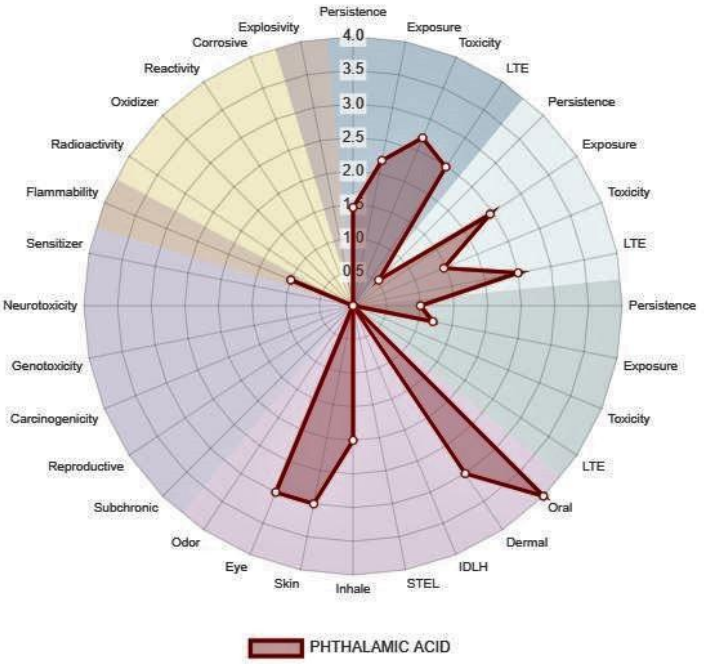
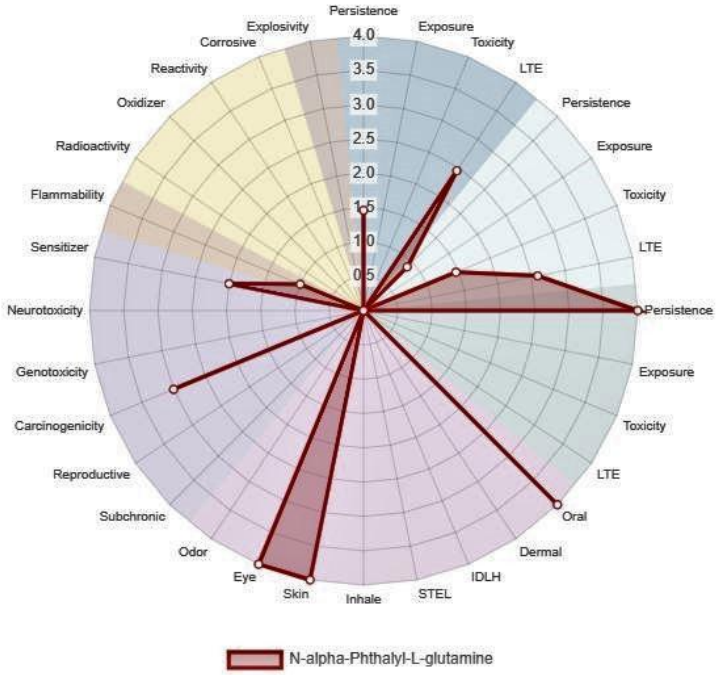
Pomalidomide



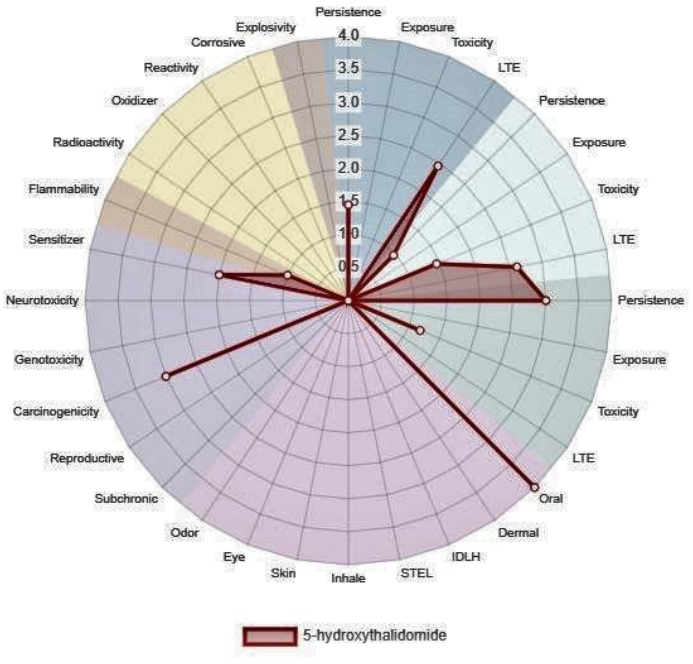
Phthalamic acid



N-Phthaloylglutamine



5-Hydroxythalidomide



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Key issues shown by the toxicity profile graphs of the molecules

(screenshot from ViridisChem's Chemical Analyzer)

Name	Thalidomide	Lenalidomide	Pomalido	PHTHALAMIC ACID	L-glutamine	5-hydroxythalido
Final Score	1.45	0.99	1.17	1.39	1.26	1.31
–Ecological Score	1.15	0.36	0.58	0.97	0.74	0.82
–Water Score	2.35	2.19	2.19	2.15	1.89	1.88
Persistence	1.44	1.43	1.43	1.46	1.46	1.45
Exposure	2.15	N/A	N/A	2.20	N/A	N/A
Toxicity	4.00	3.00	3.00	2.70	N/A	N/A
Long Term Effect	2.44	2.45	2.45	2.48	2.45	2.45
+Air Score	0.93	1.57	1.56	1.48	1.50	1.54
+Soil Score	0.70	0.01	0.06	0.29	0.15	0.19
–Health Score	2.63	2.63	2.81	2.77	2.71	2.71
–Acute Health Score	2.63	2.63	2.91	2.77	3.00	3.00
Oral LD50	2.00	2.00	3.00	3.00	3.00	3.00
Dermal LD50	2.00	2.00	2.00	3.00	N/A	N/A
Inhalation LC50	N/A	N/A	N/A	2.00	N/A	N/A
Skin Irritation	3.00	3.00	3.00	3.00	N/A	N/A
Eye Irritation	4.00	4.00	4.00	3.00	N/A	N/A
–Chronic Health Score	2.62	2.62	2.71	N/A	2.45	2.45
Subchronic Toxicity	N/A	N/A	N/A	N/A	N/A	N/A
Reproductive Effect	3.00	3.00	3.00	N/A	N/A	N/A
Endocrine Disruptor	N/A	N/A	N/A	N/A	N/A	N/A
Carcinogenicity	3.00	N/A	3.00	N/A	3.00	3.00
Genotoxicity	N/A	3.00	3.00	N/A	N/A	N/A
Neurotoxicity	N/A	N/A	N/A	N/A	N/A	N/A
Sensitizer	2.00	2.00	2.00	N/A	2.00	2.00

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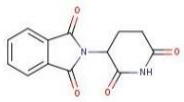
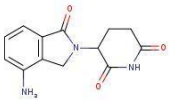
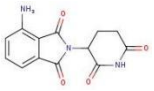
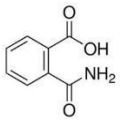
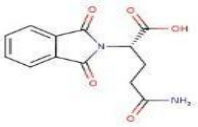
Summarized toxicity scores of the molecules (extracted from the table above)

Chemical	CAS#	Structure	Acute Toxicity	Chronic Toxicity	Ecological toxicity
Thalidomide	50-35-1		2.63	2.62	1.15
Lenalidomide	191732-72-6		2.63	2.62	0.36
Pomalidomide	19171-19-8		2.91	2.71	0.58
Phthalamic acid	88-97-1		2.77	N/A	0.97
N-Phthaloylglutamine	3343-29-1		3.0	2.45	0.74
5-Hydroxythalidomide	64567-60-8		3.0	2.45	0.82

It is evident from the detailed scores shown in the tables above that each of these closely related molecules have considerable toxicity issues. However, a closer look at the specific endpoint toxicity of the molecules, it seems that the metabolite 5-Hydroxythalidomide shows less severe acute and chronic health issues and has a better ecological toxicity footprint. According to the Human Metabolome database (HMDB), for people that have used or taken Thalidomide, it is found in human liver and kidney tissues, and has also been detected in multiple biofluids, such as urine and blood.

It is also interesting to note that the analog Lenalidomide shows a similar, although much less severe, toxicity footprint as Thalidomide.

Some key physical and toxicological properties that influence the ecological and acute health scores obtained through the Chemical analyzer may offer some helpful insights for the scientists.

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Key Physical and toxicological properties that influence the scores

	Thalidomide	Lenalidomide	Pomalidomide	Phthalamic acid	N-Phthaloylglutamine	**5-Hydroxythalidomide**
MW	258.23	259.27	276.25	165.15	276.25	274.23
BP(^{0C})	632.99	614.0	675..45	380.38	581.96	667.71
VP (mm/hg)	14.0	13.0	16.0	-	-	-
LogP	0.33	-	-1.605	-1.73		
Flashpoint	262.1	267.93	292.95	216.93	352.66	424.04
LC50 (air)	0.0	0.0	0.0	0.0	0.0	0.0
LC50 (water)mg/L	0.92	1.64	1.16	2317.5		
LC50 Soil						3293.33
LD50(oral)	112.99					
LogBAF	0.04	0.05	-0.05	-0.01	-0.04	-0.05
Log BCF	0.50	0.50	0.50	0.50	0.80	0.50
LogBTF	-0.76	-2.96	-1.81	-1.83	-1.57	-1.86
LogKOA	7.64	13.30	16.57	6.31	16.12	17.54
LogKOC	4.38	0	1.00	3.03	0	0

As more validated models related to acute and chronic health toxicity become available (developed in-house, or through third-party partnerships), ViridisChem is committed to make them available through its platform.

There are many advantages of knowing most properties of a molecule and the severity of the various (about 54) endpoints that together show the ecological, health, and safety related toxicity:

- Based on the application of the drug molecule (in-vitro, in-vivo) and its therapeutic target, scientist can decide which toxicity will render the molecule unusable for their application, or which toxicity would be tolerable
- Having the information about the molecule's analogs and metabolites, scientists have more options to decide whether they should pursue the research of the target molecule, or focus on less toxic analog(s) or metabolites
- Having 48 different physical and toxicological properties per molecule and identifying the potential acute and chronic health issues, toxicologists are equipped with lot of preliminary information that otherwise they would have to collect from various sources to define their study plan saving them weeks' worth of effort

For more information about ViridisChem platform and products, please refer to the company's website: https://www.viridischem.com or contact us at support@viridischem.com

References:

1. "Structural basis of thalidomide enantiomer binding to cereblon" by Tomoyuki Mori, Takumi Ito, Shujie Liu, et.all; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778007/

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