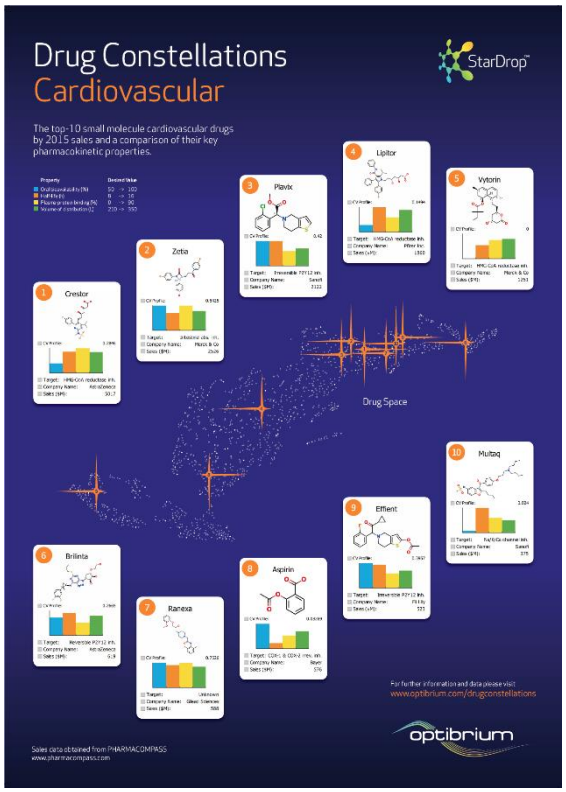
Drug Constellations:

Overview



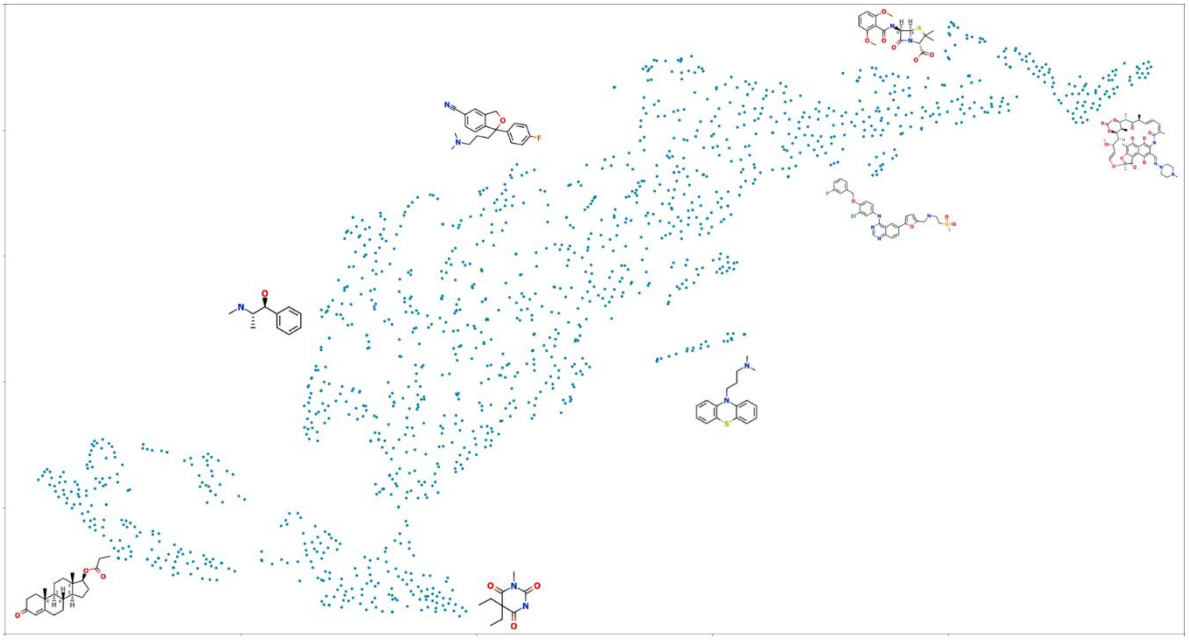
Optibrium's Drug Constellations provide an instant, visual summary of the top-selling small-molecule drugs for a therapeutic indication. The top-ten drugs for each indication are mapped across the 'chemical space' of all marketed drugs. A summary of market and target data is provided for each compound, along with an assessment of its pharmacokinetic properties against a profile of criteria that are relevant to the therapeutic indication.

The first of the constellations in this series depicts the top-ten drugs for cardiovascular indications. If you'd like a high quality printed version of this constellation, please contact us and we will be happy to send you a copy.

Below, we provide more details about how the drug space was created, the choice of property criteria against which the pharmacokinetic properties of the compounds were assessed and the detailed data used for each compound, along with references for the sources.

Drug Space

This 'drug space' was generated using StarDrop's chemical space visualisation using a set of 1395 marketed small molecule drugs. In this space, the proximity of two points represents the structural similarity between the corresponding compounds. This provides a convenient way to map the distribution of compounds or their properties across the chemical diversity of drugs. The figure below shows some illustrative structures for different regions of the space.



Technical Details

In generating this space, the similarity between two compounds is defined using a Tanimoto index based on a 2D path-based fingerprint. The distribution of points is generated using the t-distributed stochastic neighbour embedding algorithm [1].

Data set

The compound structures used to create the drug space were downloaded from the ChEMBL approved drug list [2]. Only compounds assigned a 'Development Phase' of 4 were retained. Duplicate structures and compounds with molecular weight less than 100 Da or greater than 1000 Da were removed.

StarDrop users can download a Drug Space StarDrop project containing this data set and plot their compounds into the same drug space.

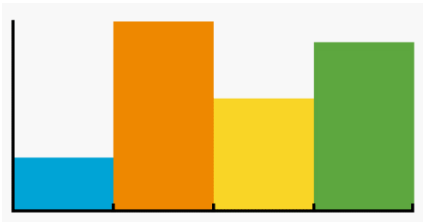
Pharmacokinetics Scoring Profile

Each of the top-10 cardiovascular (CV) compounds were scored using StarDrop's Probabilistic Scoring approach [3] for multi-parameter optimisation. This assesses the overall balance of properties against a profile of criteria representing the desired properties of a high quality compound for the therapeutic objectives of a project. The overall score, between 0 and 1, represents the likelihood of achieving the ideal outcome for all properties.

The top-10 cardiovascular drugs were scored based on their clinically observed pharmacokinetic (PK) properties:

- Oral bioavailability (%)
- Half-life (h)
- Plasma-protein binding (%)
- Volume of distribution (L)

For each compound, a histogram shows the performance of each of these properties against the desired property values, as illustrated right.

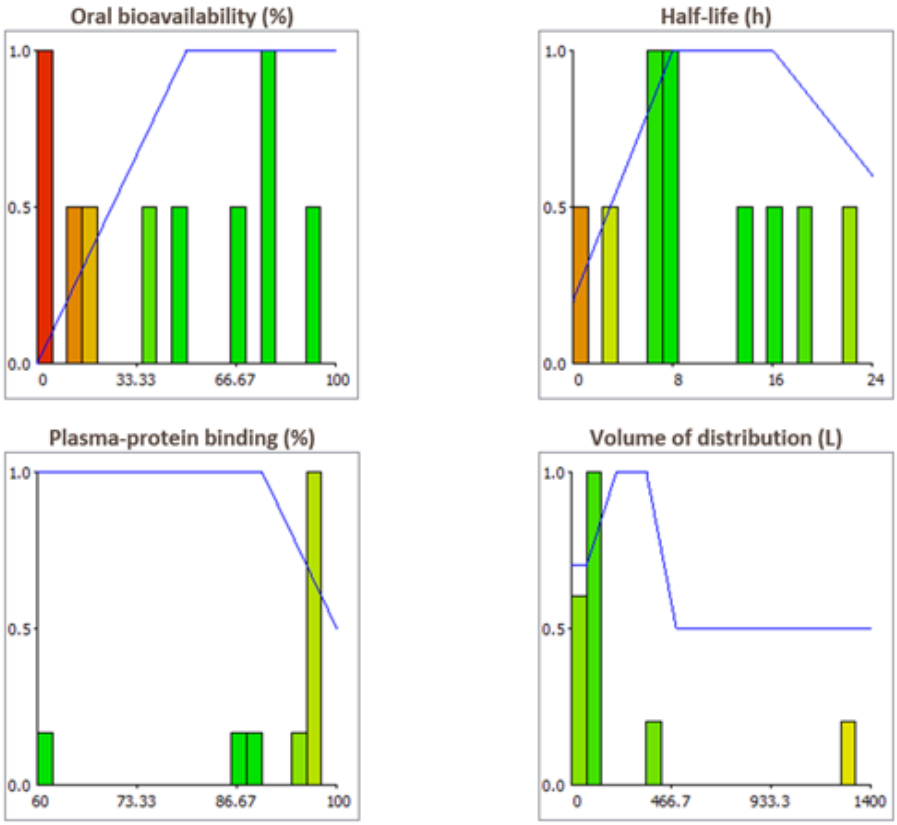


A high bar for a property indicates a good value of the property while a low bar corresponds to a poor value against an important property criterion. The data for each of the compounds, along with references to the sources, are provided in the table in the Data section below.

The scoring profile used to compare the top-ten CV compounds was as follows:

Property	Desired Value	Importance
Oral bioavailability (%)	50 -> 100	
Half-life (h)	8 -> 16	
Plasma-protein binding (%)	-inf -> 90	
Volume of distribution (L)	210 -> 350	

The range of desired values for each of the properties is shown above, along with the relative importance of each property criterion. However, the criteria are not defined as hard cut-offs, which could draw artificially harsh distinctions between compounds with similar property values near to the boundaries of the desired ranges. Instead, a 'desirability function' has been defined for each criterion, relating the value of each property to its desirability. The desirability functions used in this profile are shown below (in each case the desirability function is shown in blue and the histogram shows the distribution of the corresponding property values for the top-10 CV compounds):



This scoring profile is included in a CV top-10 StarDrop project which StarDrop users can download to score their own compounds, or modify as required.

The choice of a property profile is subjective to some degree, but the rationales for the choice of these desirability functions are as follows:

- For an orally dosed compound, high oral bioavailability is desirable to achieve good systemic exposure. Typically, a value above 50% would be ideal, but below this, the higher the oral bioavailability the better. A value of zero is clearly unacceptable.
- A half-life between 8 and 16 hours would be suitable for twice-daily dosing. A half-life below this would increase the likelihood of requiring a larger number of doses or a larger dose to maintain a therapeutic concentration. Requiring a higher number of doses increases the risk of poor patient compliance, while administration of large doses would require a high therapeutic index. A half-life above 16 hours increases the risk of accumulation, potentially leading to toxicity. This was considered a lower risk, so a high half-life is given a lower penalty than a low half-life in the desirability function for this property.
- High plasma-protein binding reduces the free concentration of a compound; therefore, plasma-protein binding values close to 100% are undesirable. However, very low plasma-protein values are difficult to achieve; therefore, a desired range of less than 90% is defined.
- A volume of distribution above 70L indicates distribution within total body water, hence a value greater than this would be desirable, with an ideal range between 210L and 350L, indicating good tissue exposure. A much higher volume of distribution indicates a greater degree of non-specific binding, increasing the risk of toxicity or undesirable pharmacology; therefore, values above 350L are assigned decreasing desirability, with values above 490L given the lowest desirability.

Of course, there is no single 'ideal' pharmacokinetic profile for a CV drug and there are certainly exceptions to these 'rules'. For example, Simvastatin is a component of Vytorin and has very low oral bioavailability. However, Simvastatin is a pro-drug and is converted almost entirely to the active beta-hydroxy form by first-pass metabolism. Therefore, poor oral bioavailability is acceptable for the parent because exposure to the active metabolite is good.

Drug Data

Sales Rank	Product Name	Company Name	Active Ingredient	Target	Oral bioavailability (%)	Volume of distribution (L)	Plasma-protein binding (%)	Half-life (h)	Sales ($M)[1]
1	Crestor	AstraZeneca	Rosuvastatin Calcium	HMG-CoA reductase inh.	20 [4]	134 [4]	88 [4]	19 [4]	5017
2	Zetia	Merck & Co	Ezetimibe	Intestinal abs. inh.	93 [5]	105 [6]	90 [5]	22 [7]	2526
3	Plavix	Sanofi	Clopidogrel Bisulfate[2]	Irreversible P2Y12 inh.	>50 [8]	33 [9]	98 [8]	8 [8]	2122
4	Lipitor	Pfizer Inc.	Atorvastatin Calcium	HMG-CoA reductase inh.	14 [10]	381 [10]	98 [10]	14 [10]	1860
5	Vytorin	Merck & Co	Ezetimibe and Simvastatin[3]	HMG-CoA reductase inh.	0 [22]	116 [11]	95 [12]	3.5 [11]	1251
6	Brilinta	AstraZeneca	Ticagrelor	Reversible P2Y12 inh.	36 [13]	116 [13]	99.7 [13]	7 [13]	619
7	Ranexa	Gilead Sciences	Ranolazine	Unknown	76 [14]	132.5 [15]	62 [14]	7 [14]	588
8	Aspirin	Bayer	Acetylsalicylic Acid	COX-1 & COX-2 irrev. Inh.	68 [16]	10.5 [17]	99.5 [18]	0.25 [18]	576
9	Effient	Eli Lilly	Prasugrel[4]	Irreversible P2Y12 inh.	79 [19]	56 [20]	98 [20]	7.4 [20]	523
10	Multaq	Sanofi	Dronedarone	Na/K/Ca channel inh.	4 [21]	1400[5] [21]	98 [21]	16 [21]	375

These data can be downloaded in a CV top-10 StarDrop project along with the compound structures and scores.

[1] Sales data obtained from PHARMACOMPASS, www.pharmacompass.com.
[2] Clopidogrel is a prodrug. Therefore, the half-life and volume of distribution are presented for the active metabolite.
[3] Pharmacokinetic and target data shown for Simvastatin. Data for Ezetimibe is shown above.
[4] Pasugrel is a prodrug and is rapidly and extensively converted into its active metabolite. Therefore, PK data is presented for the active metabolite.
[5] The intravenous volume of distribution is shown.

Notes

- Zetia (Ezetimibe) is absorbed and conjugated to a phenolic glucuronide which is the subject of enterohepatic recirculation. As an intestinal absorption inhibitor, this increases the exposure at the site of action and leads to a prolonged half-life.
- Plavix (Clopidogrel) is a prodrug and is converted into its active carboxylic acid metabolite by cytochrome P450 metabolism. For this reason, the half-life and volume of distribution of the active metabolite are shown because they are more relevant to its efficacy.
- Vytorin is a combination therapy of Ezetimibe and Simvastatin. Ezetimibe is represented individually in the top-10; therefore, the PK data for Vytorin represents the properties of Simvastatin. Simvastatin is a prodrug and is extensively metabolized into the active beta-hydroxy metabolite on first pass; therefore, the low oral bioavailability of the parent compound is, in practice, not a liability for this drug.
- Effient (Prasugrel) is a prodrug and is extensively metabolised on first pass to form its active metabolite; therefore, the PK data for the active metabolite are shown because they are more relevant to its efficacy.

References

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About Optibrium

Optibrium provides elegant software solutions for small molecule design, optimisation and data analysis. Optibrium's primary product, StarDrop™, brings confidence to the selection and design of high quality candidate compounds.

Founded in 2009, Optibrium continues to develop new products and research novel technologies to improve the efficiency and productivity of the drug discovery process. Optibrium works closely with its broad range of customers and collaborators that include leading global pharma, agrochemical and flavouring companies, biotech and academic groups.

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