Drug Constellations

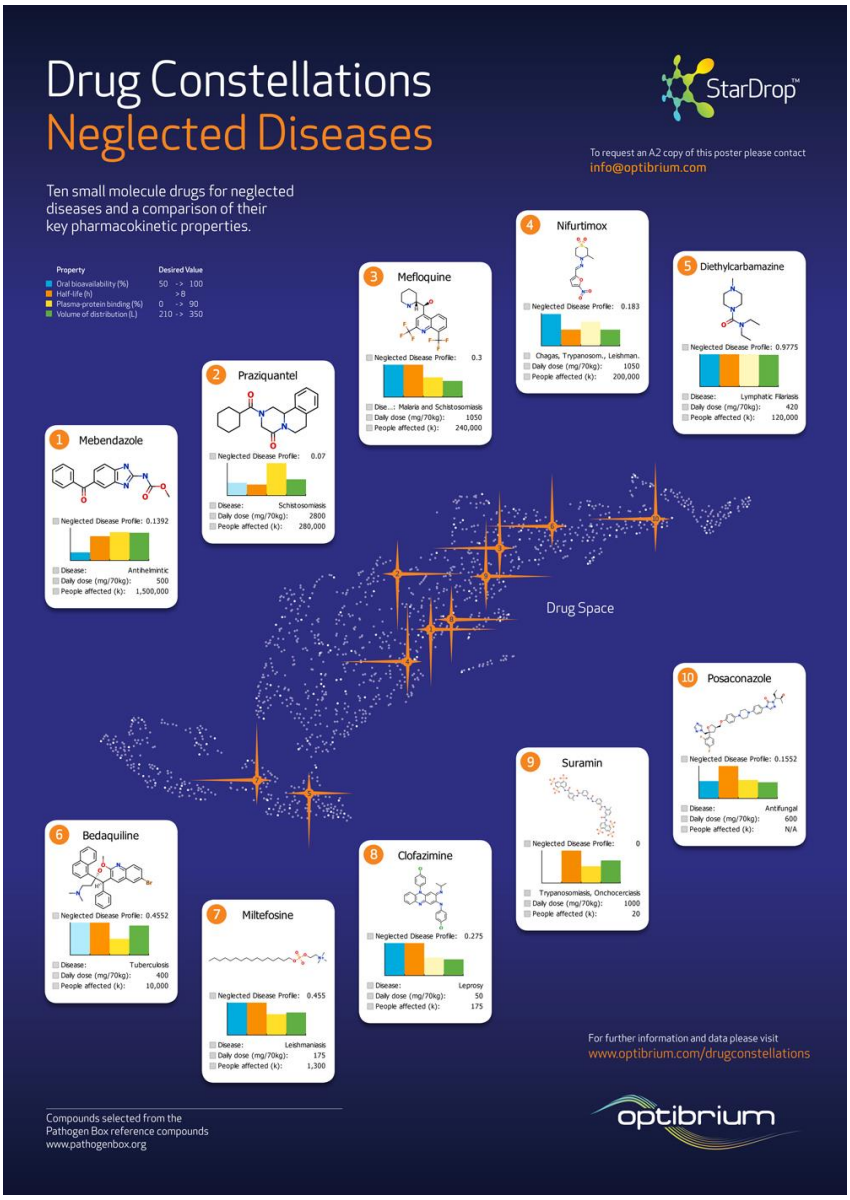
Neglected Diseases

Optibrium's drug constellations provide an instant, visual summary of important small-molecule drugs for a therapeutic class or indication. Ten drugs for each indication are mapped across the 'chemical space' of all marketed drugs. A summary of key 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.

This constellation describes important drugs for neglected diseases. These were selected from the set of reference compounds published with the Pathogen Box. For more information, please visit http://www.pathogenbox.org/.

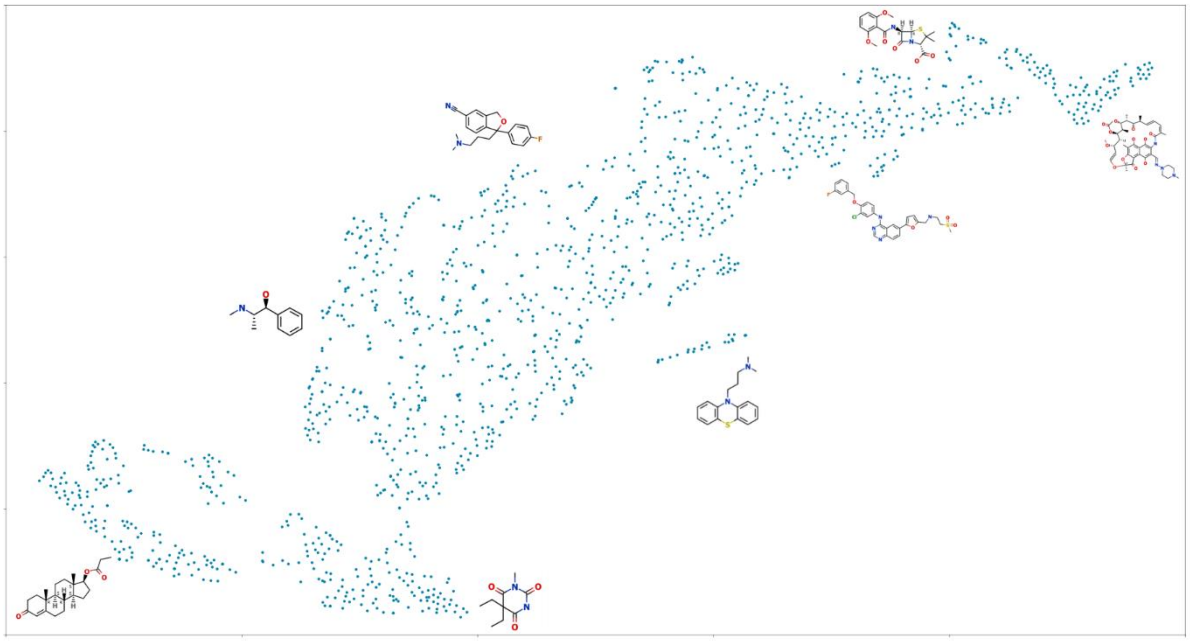
If you'd like a high quality printed version of this constellation, please contact us and we would be happy to send you a copy.

Below we provide more details of 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.



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 neighbor embedding algorithm [1].

Data set

The compound structures used to create the drug space was 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.

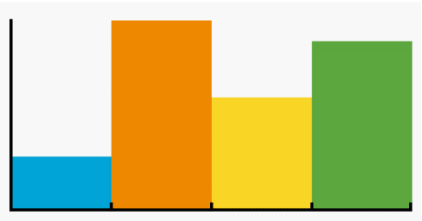
Pharmacokinetics Scoring Profile

Each of the 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 ten 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.

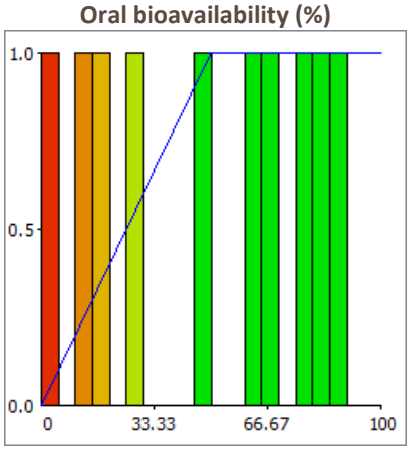
In some cases, a bar in a histogram is 'greyed out' indicating that the contribution of this compound is based on highly uncertain or missing data. For details, please see the table of detailed information for each compound below.

The scoring profile used to compare the ten compounds for neglected diseases was as follows:

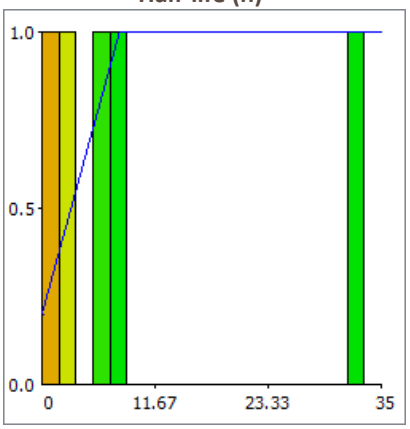
Property	Desired Value	Importance
Oral bioavailability (%)	50 -> 100	
Half-life (h)	8 -> inf	
Plasma-protein binding (%)	-inf -> 90	
Volume of distribution (L)	210 -> 350	

The range of desired values for each of the properties are 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 for the ten neglected diseases compounds):

Oral bioavailability (%)

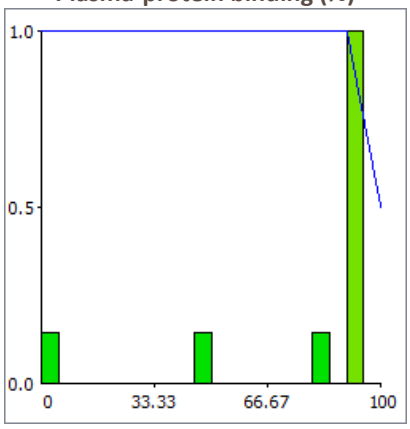


Half-life (h)[1]

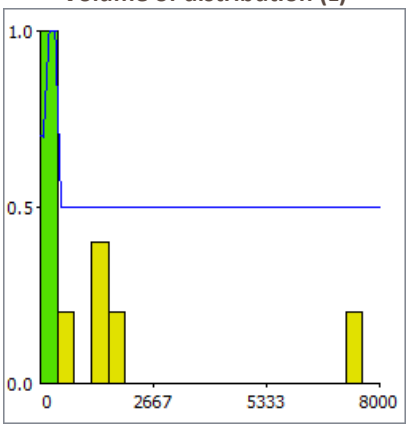


[1] Only lowest 5 half-life compounds are shown on histogram for scale. Some compounds have half-life >100 hours.

Plasma-protein binding (%)



Volume of distribution (L)



This scoring profile is included in a Neglected Diseases 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 above 8 hours would be suitable for dosing no more frequently than twice-daily. A half-life below this would increase the likelihood of requiring 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. Due to the challenges of supply and compliance in developing nations, less frequent dosing may be desirable and, in some cases, a single dose treatment would be ideal. Hence, longer half-lives are not penalised, despite the risk of accumulation, potentially leading to toxicity.
- 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 70 L indicates distribution within total body water, hence a value greater than this would be desirable, with an ideal range between 210 L and 350 L, 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 490 L given the lowest desirability.

Of course, there is no single 'ideal' pharmacokinetic profile for a drug for a neglected disease; there are variations in the preferred profile for specific diseases and there are certainly exceptions to these 'rules'.

Drug Data

Name	First Discovered or Approved	Disease(s)	Estimated Number of people affected[2] (k)	Daily Dose (mg/70kg)	Oral bioavailability (%)	Volume of distribution (L)[3]	Plasma-protein binding (%)	Half-life (h)
Miltefosine	1980	Leishmaniasis	1,300	175	N/A[4]	49 [4]	96-98 [4]	150-200 [5]
Posaconazole	2005	Antifungal	N/A	600	N/A[5]	1,774 [6]	>98 [6]	35 [6]
Suramin	1920	Trypanosomiasis and Onchocerciasis	20	1000	N/A[6]	20.6 [7]	99.7 [8]	864-1440 [8]
Clofazimine	1986	Leprosy	175	50	70 [9]	1,470 [10]	High [11]	240 [9]
Bedaquiline	2012	Tuberculosis	10,400	400	N/A	164 [12]	>99.9 [12]	3,500 [13]
Diethylcarbamazine	1947	Lymphatic Filariasis	120,000	420	80-85 [14]	200 [15]	Negligible [16]	8 [16]
Nifurtimox	1965	Chagas disease, Trypanosomiasis, and Leishmaniasis	205,000	1,050	50-79 [17]	755 [18]	N/A	3 [18]
Mefloquine	1970	Malaria and Schistosomiasis	240,000	1,050	89 [19]	1,400 [20]	98 [20]	336-672 [20]
Praziquantel	1982	Schistosomiasis	258,000	2,800	Low [21]	8,000 [22]	80-85 [22]	2 [21] [23]
Mebendazole	1971	Antihelmintic activity	1,500,000	500	2-22 [24] [25]	142.1 [24]	90-95 [26]	5.5 [26]

These data can be downloaded in a Neglected Diseases StarDrop project along with the compound structures and scores.

[2] According to the World Health Organisation or Wikipedia
[3] Assuming a 70 kg patient
[4] Not measured due to haemolysis (high in rats and dogs)
[5] No IV formulation, therefore absolute bioavailability cannot be determined
[6] Administered intravenously

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