# Application of *in Silico* (ADMEnsa Interactive) and ADME/PK Assays in the Identification of New Chemical Entities (NCEs) for Pre-Clinical Evaluation

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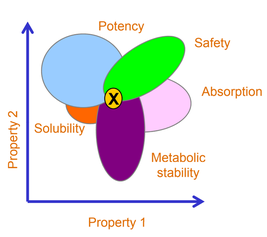
## Abstract

The current paradigm of drug discovery utilising chemical library synthesis coupled with high throughput screening technologies often gives rise to a situation whereby drug discovery programmes are compound rich although poor in ADME properties. As such, the ADME properties of compounds require optimisation, through the phases of lead optimisation, prior to progression for clinical development increasing the cost and duration of the process. A prime driver of drug discovery is therefore the early identification of compounds from diverse chemical spaces with optimal ADME properties.

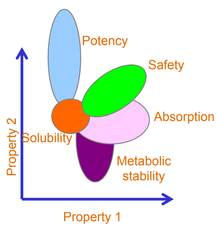
ADMEnsa Interactive is an *in silico* suite of software which enables an estimation of a compounds likelihood of success based upon a balance of the ADME properties required to meet a product profile within a diverse range of therapeutic areas. Prior to initiation of chemical synthesis the key ADME and physicochemical parameters may be predicted from a virtual screening strategy. With the initiation of chemical synthesis, any potential ADME limitations flagged by the *in silico* predictions can be given priority testing in the ADME/PK laboratory. Using such information SAR relationships may be established leading to the rapid, cost effective, identification of high-quality potential new chemical entities (NCEs) suitable for pre-clinical evaluation. Examples will be presented demonstrating the use of AI and experimental generated ADME data in the identification of NCEs suitable for progression to pre-clinical evaluation.

## Introduction

It is widely accepted that a successful drug must exhibit not just potency, but a balance of a several other properties. As such, the drug discovery process is an attempt to find a 'sweet spot' in chemical space in which all the necessary properties can be simultaneously optimised.
Hit molecules typically lie in the 'potent' area of chemical space, but may not have all of the other necessary properties for a successful drug. The goal is often to move as efficiently as possible from an area of potency to the 'sweet spot.'




Identify chemistries with an optimal balance of properties



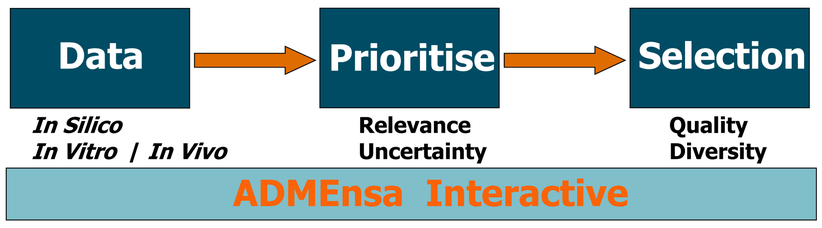

Quickly identify situations when such a balance is not possible

Given that it is not always possible to find a molecule that has the required balance of properties it is important to be able to identify such situations as efficiently as possible. One way to achieve this is to use *in silico* methods to profile as broad an area of chemical space before focussing on those areas most likely to succeed to confirm these findings experimentally.

ADMEnsa Interactive (AI) is a software tool that may be used by ADME scientists and medicinal chemists to help rapidly identify those compounds with the best ADME parameters throughout the drug discovery pipeline from hit to lead to pre-clinical candidate. Within the process, *in silico* predictions of ADME properties can be used alongside measured properties to identify compounds that have the greatest overall chance of meeting all of the project requirements.

## Applying Data to Make Decisions

The key to the ADMEnsa approach is that value is created by good decisions that progress a project toward its goal, not by the data itself. As such, ADMEnsa Interactive has been designed to assist the user through the decision making process.




### Data

At the earliest stages of a project the only available data will be from *in silico* sources that can be used to assess virtual compounds. As the project progress this will gradually be accompanied by and the superseded by increasingly high quality in vitro and *in vivo* data.

### Prioritise

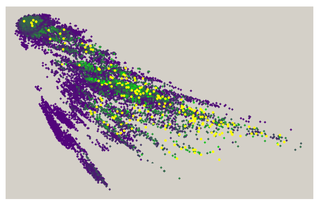
With a set of data available, the next step is to prioritise the compounds to identify those with the best balance of properties. This depends both on the **relevance** of each property to the ultimate therapeutic objective of the project and the **uncertainty** in the data, as every data point, whether predicted or experimental will have some amount of statistical or experimental error. During the scoring process more weight will be applied to the higher priority properties.

Using **probabilistic scoring**, the user builds a scoring profile defining the ideal value of each property and its relative priority, to generate a score indicating each compound's likelihood of success given the uncertainties in the data. This scoring profile using a number of *in silico* properties might be used for an oral CNS target.

| Models | Required values | Priority |
|---|---|---|
| Aqueous solubility | >10µM | |
| Absorption (HIA) | + (> 30%) | |
| Log ([brain]:[blood]) | >-0.5 | |
| P-gp transport | non substrate | |
| hERG Affinity (pIC50) | <6.0 | |

### Selection

The final step is to select the compounds to be synthesised or progressed to further rounds of testing. This should be based on the quality of the compounds, which is the information produced at prioritisation stage. However, it is important not to ignore chemical diversity, especially at the early stages of a project where it is useful to generate data on a wide chemical diversity to spread risk across multiple chemotypes and generate information on SAR.



Using **chemical space** and **selection** tools the user can explore selections to find an appropriate balance between the compounds with best overall score and the greatest diversity. The diagram shows a chemical space of a large library in which the best compounds are green, the worst are purple and the selection is highlighted in yellow. In the example, the bias was 75:25 between diversity the best scoring compounds. It can be seen that the selection covers a large area of the overall chemical space, missing out only a small number of clusters in which nearly all the compounds score badly.

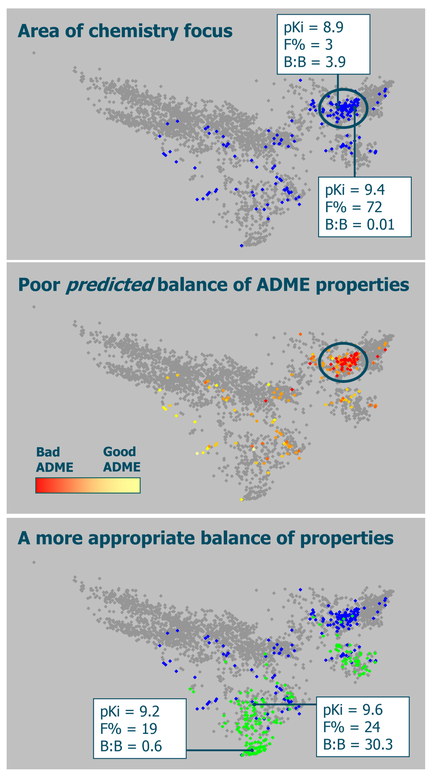
In the following case study, ADMEnsa Interactive was used to apply this process at each key decision making stage where selections of compounds were made for progression.

## Case Study: Reducing Synthesis Cycles in Lead Optimisation

### Background

ADMEnsa was asked to help a client with a difficult project to identify an orally bioavailable therapy for a CNS target. To date, they had not identified an active compound that had an acceptable combination of both oral bioavailability and CNS penetration. The client provided ADMEnsa with all project data and wanted to know how ADMEnsa Interactive could have helped them to identify suitable compounds at an earlier stage and how much resource its application would have saved.

In consultation with the client, an analysis of existing project data was performed to establish the major decision criteria for compound progression. The chronological progress of the project towards its target project profile was then charted.




The first 200 compounds progressed to *in vitro* ADME profiling (blue) were predominantly in one discreet area of chemical space. This was where the most potent compounds were located. However, as can be seen by the two examples, compounds in this area typically possessed either good bioavailability or good CNS penetration, but not both. In striving for greater potency the project chemists had isolated themselves in an area of chemistry that was unlikely to yield successful compounds.

A scoring profile was created in ADMEnsa Interactive to identify those compounds having the best overall balance of ADME properties based on *in silico* predictions. On this chemical space, high scoring compounds are coloured in light yellow and those with a poor predicted balance of ADME properties are coloured in red. Had this *in silico* analysis been carried out prior to compound synthesis, it would have highlighted the difficulties in this area of chemical space, potentially saving "misdirected" resource.

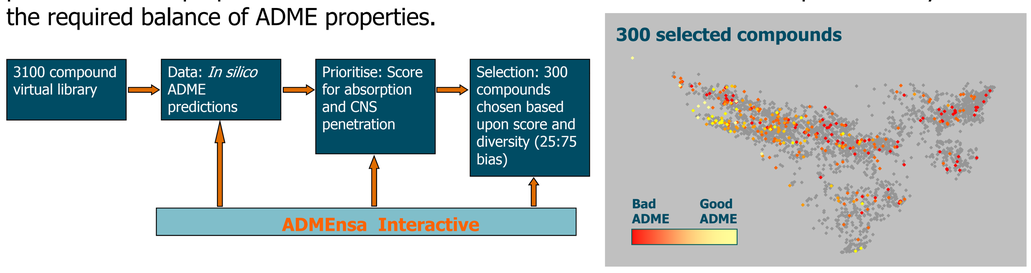
The second 200 compounds progressed to in vitro ADME profiling (green) showed a marked change in synthetic focus. Compounds in the lower region of the chemical space maintained good levels of activity but had a much better balance between bioavailability and CNS penetration as illustrated by the two compounds highlighted. However, to get to this point the client had synthesised and screened in excess of 3000 compounds, 400 compounds were progressed to *in vitro* ADME and 70 progressed to *in vivo* pharmacokinetic analysis.

### Objective

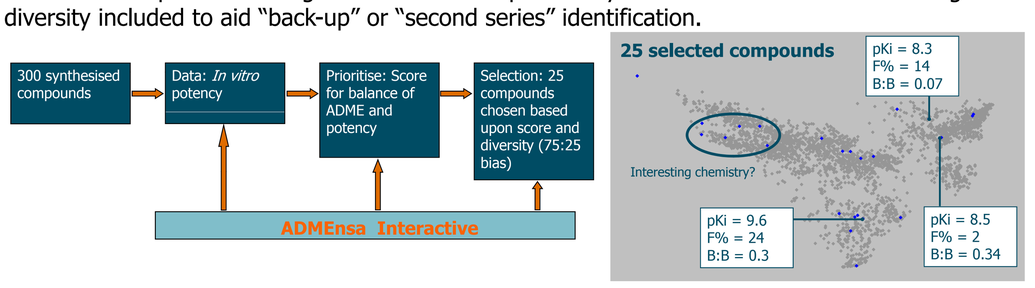
To perform a retrospective analysis of the project with the end point of selecting 25 compounds for *in vivo* pharmacokinetic analysis from an initial virtual library of 3,100 molecules.

### Process

An initial subset of 300 compounds would be selected from the virtual library. Although the library had been designed with target activity in mind, little is known about the potency SAR and initial compound selection needed to cover a wide chemical space in order to identify diverse hits. However, by using ADMEnsa Interactive it was possible to profile the entire library for predicted ADME properties and include in the selection a bias towards compounds likely to have the required balance of ADME properties.




The selected compounds would then be synthesised and screened for *in vitro* potency. Assuming that the library contained a significant number of hits (in this retrospective analysis we knew that this was the case), compounds were then scored again; this time for an appropriate balance between good potency (measured) and good ADME (predicted). A further subset of 25 compounds would then be selected for progression *in vivo*. Here the bias in the selection was in favour of compounds having the best overall probability of success but with some degree of diversity included to aid "back-up" or "second series" identification.




Whilst *in vivo* PK data are not available on all of the ADMEnsa selected compounds, it can be seen in the above plot that the approach selected key compounds that summarise the progress of the project in relation to its ADME target profile and also highlighted an area of space previously overlooked by the project team.

## Conclusion

The application of ADMEnsa Interactive to this project could have resulted in a 90% saving in compounds synthesised. No *in vitro* ADME screens were used in the selection process and, furthermore, a 70% saving in *in vivo* testing was achieved to reach the same endpoint.
At each stage, the key steps to enable this were to consider what data were available and the relevance of those data to the project aims. With this it was then possible to make selections considering the quality of the compounds and their diversity, allowing the project to rapidly focus into the most appropriate area of chemical space.

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