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Concept Articles

Kepner-Tregoe Decision Analysis as a Tool to Aid Route Selection. Part 1

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Abstract:

Kepner-Tregoe Decision Analysis is a logic-based tool that has been used by AstraZeneca to prioritise the investigation of alternative routes to drug candidates. This paper describes how the tool can be used in route selection work, with subsequent papers discussing application to AstraZeneca projects.

Introduction

The investigation of alternative routes to drug candidates is an important task for Process Research and Development (PR&D) departments. In the majority of cases, the route used by Medicinal Chemistry to supply small amounts of compound is not suitable for intermediate and large-scale supply because of issues such as safety, economics or accommodation restrictions.

When considering alternative routes, time and resource available is often less than would be needed to investigate all the possibilities, and a selection process is required to choose the best routes and prioritise the work. When conducting such exercises, the PR&D Department at AstraZeneca has developed the use Kepner-Tregoe Decision Analysis to facilitate this activity.

The Kepner-Tregoe system[1] is a collection of logic-based problem-solving and decision-making tools, including situation appraisal and potential problem analysis. The tools have been used across a wide range of organizations, most famously helping NASA with the problems encountered on the Apollo 13 mission.

Decision analysis is one of the tools available from the Kepner-Tregoe system. This tool allows the evaluation of alternatives against an agreed framework, thus providing an impartial prioritisation process.

Following the use of Kepner-Tregoe Decision Analysis in other business areas, it was decided to evaluate the tool to aid route selection work.

Kepner-Tregoe Decision Analysis

Kepner-Tregoe Decision Analysis proceeds through a set of defined steps, allowing a balanced choice to be made. The steps are outlined below, with details about how the system may typically be applied to route selection.

State the Decision. The first activity in the sequence is to define the intended result of the decision. Thus, a short decision statement is prepared, concisely defining the reasons for and requirement of the decision being made. A generic decision statement for investigating alternative routes to a drug candidate could read “To identify routes for the long-term manufacture of the required drug candidate, paying particular attention to critical factors (e.g., safety, environmental, cost, intellectual property, etc.).”

The decision statement helps to keep the decision makers on track, defining what needs to be decided and what is being achieved.

Develop Objectives. At this stage of the process, criteria that will influence the choice need to be defined to help evaluate the alternatives fairly. The most important criteria for individual projects are likely to be have been identified in the decision statement, but all other factors should be listed.

Numerous criteria influence the choice of a synthetic route, and these will vary from project to project. A number of criteria that may influence the choice have been compiled across a number of projects and are listed in Table 1.

Not all the criteria listed in Table 1 will be relevant to a particular project, and a selection should be made, choosing only those that are pertinent. For a typical project, between 6 and 12 criteria may be selected.

Classify Objectives into Musts and Wants. Following the selection of a list of objectives, these are categorised into “Must” criteria (Musts) and “Want” criteria (Wants).

Musts are those that are mandatory and need to be met for an option to be considered. In route selection, some obvious Musts are objectives such as safety, health and environment (route must have no insurmountable issues in these areas), intellectual property (route must have freedom to operate) and raw materials availability (it must be possible to purchase the necessary raw materials for the route in bulk quantities).

All other objectives are Wants. These criteria do not need to be met for a route to be considered, but their relative importance and how well each option scores against them is the key method of comparing the different possibilities.

Weigh the Wants. With a list of Must and Wants defined, the relative importance of the Wants is defined. This determines how much each Want will influence the decision being taken. Considering the available list, the most important Wants are identified and scored 10, with the remaining Wants scored

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Table 1. Route criteria

criteria	explanation
accommodation	Are there any steps that would be difficult to accommodate?
back-ups	Is the route applicable to any back-up compounds?
chemical feasibility	How likely are the proposed reactions to work?
chiral integrity	How well will any chirality survive transformations in the route?
chirality	What is the enantiomeric excess of any introduced chiral centres?
convergence	How convergent is the route?
cost of goods	What is the cost of goods for the route?
effluent	What is nature of the effluent cost of disposal?
environment	Do any of the steps on the route pose a significant environmental hazard?
flexibility	Will the route allow delivery of different compounds if the choice has not been narrowed down to one?
health	Do any of the steps on the route pose a significant health hazard?
intellectual property	Are there any intellectual property issues or opportunities?
meets existing API specification	Will the route afford material that meets the existing API specification?
number of steps	How may chemical steps does the route contain?
number of steps to key step	How much time/effort is required to investigate the key step on a route?
potential genotoxic impurities	Are there any issues with potential genotoxic impurities on the route?
potential yield (overall/individual step)	What is the potential yield of individual stages? What is the potential overall yield? (Data can be updated as experimental work is completed.)
purification points	How many, and where, are the purification points on the route?
raw material availability	Can the required raw materials be sourced in bulk?
robustness	Are the chemical transformations robust?
safety	Are all the transformations on the route safe to operate?
solubility of intermediates	Are there any issues with the solubility of any intermediates?
throughput	What is the throughput of route?

between 9 and 1 depending on their importance relative to the most important Wants.

Generate Alternatives. The focus of the decision process now turns to identifying or creating possible choices. For route selection activities, this will normally involve brainstorming and detailed literature searching. Asking for contributions from across the company's scientific community and discussion with appropriate consultants may also add to the available list. For simple molecules, the list of alternatives may be small, but for complex targets, particularly those with chiral centres, a large number of possible routes may be generated. Increasing the number of alternatives is of benefit, as it increases the chances of being able to pick the best options by comparison with the other routes.

Having generated a list of alternatives, the selection and ordering of the routes begins.

Screen Alternatives through the Musts. All the alternatives are evaluated against the Musts, and those that fail to meet the criteria are eliminated from the decision process. Eliminated routes may have safety, health or environmental problems that are considered insurmountable, may use intermediates that are covered in a rival's patent, or may use expensive raw materials that are not possible to source on a large scale.

Compare Alternatives against the Wants. A key activity of Decision Analysis then becomes evaluation and ranking the alternatives. For each Want that has been identified a scoring system needs established. The best options score 10, with the remaining alternatives scoring between 9 and 0.

Creating scoring systems can be a challenging activity. For some Wants, such as number of steps, setting up systems is relatively easy, with the shortest route scoring 10 and other routes being awarded lower scores as the number of steps increases. Other Wants, such as introduction of chirality, are more difficult to score. A resolution may be effective at producing material of high chiral purity, but the yield will be <50%, whereas the use of asymmetric synthetic methodology may not give as good chiral purity but will give a higher yield. Setting up scoring systems for any Want should be possible, but careful analysis is required, and it should be noted that the use of nonlinear measuring systems (logarithmic, exponential, etc.) can be useful.

Having set up a scoring system for each Want, each alternative is measured against the Want. The score obtained for an alternative is then multiplied by the weigh of the Want (vide supra) to give a weighted score. The weighted scores for each alternative are then totalled giving an overall score.

Identify Adverse Consequences. Having ranked the available options, it is important to undertake a review of the Decision Analysis, undertaking a reality check on all the alternatives, as well as those that have been eliminated. For example, some routes that looked extremely attractive on paper may have been eliminated due to failing a Must. These routes should be reviewed, and if it is possible to mitigate the issues raised by the Must, the routes can be considered further.

It should also be noted that when using Chemical feasibility as a Want, the original (normally Medicinal Chemistry) route will always score better than unproven routes, and this should be borne in mind when comparing routes. Finally, there should be some place for chemical intuition, and scientific experience may offer some additional insights into the alternative being considered.

Make the Best Balanced Choice. The overall scores for each option are then compared, and the highest scoring ones are selected. When applied to route selection, Decision Analysis will give a list of potentials which can be ordered from most to least preferred. How this data is used will be dependent on the quantity of time and resource available to the route selection team.

Review the Data. As experimental work is conducted on the selected routes, the scoring for individual routes will change (steps may need to be added or subtracted, yields that were estimated can be measured, the accommodation of particular step is simpler than expected, etc.). These changes should be applied to the Decision Analysis data, and the overall scores for the route adjusted. Additionally, new scientific developments should be taken into account, which may change the scoring of a particular route, or introduce new routes to the Decision Analysis. Such activity allows the process to be under continuous review so that reprioritisation of work can take place if necessary.

Conclusions

Kepner-Tregoe Decision Analysis is a logic-based system for prioritising options that can be applied to the selection of synthetic routes to deliver drug candidates. The system is unbiased and transparent, allowing a decision to be made on available and projected data, rather than on personal opinion and force of argument. It is hoped that this paper has effectively described the procedure used to conduct such Decision Analysis and that the examples in the following papers will further clarify the process.

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Supporting Information Available

Routes passing Musts but scoring below 249. This material is available free of charge via the Internet at http://pubs.acs.org.

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