


DRUG DISCOVERY



Selvita is the first Polish biotech company with fully integrated drug discovery platform encompassing classical medicinal chemistry, *in silico* screening, structure-based drug design, molecular and cell biology, pharmacokinetics and pharmacology, as well as custom synthesis. Our ambition and ultimate goal is to discover more effective and safer drugs to treat patients suffering from cancer and other diseases. To achieve this goal we have assembled a unique team of highly skilled professionals with broad experience from drug discovery industry in North America and Western Europe.

Therapeutic area expertise

Our current drug discovery efforts are focused on two therapeutic areas – Oncology and Central Nervous System disorders.

ONCOLOGY

In oncology, we are particularly interested in pursuing novel and less explored therapeutic targets among kinases and other signaling proteins important for cancer growth and survival.

Pim kinases are currently one of the most interesting new therapeutic targets researched by the biggest pharmaceutical companies in the world. According to the most recent literature reviews, Pim kinases are strongly related to the process of oncogenesis and development of several types of cancer including leukemias, and glioblastomas.

Our most advanced project – SEL24 – involves a group of highly potent and selective compounds which are specific inhibitors of Pim-1 kinase, with IC₅₀ at low nM concentration. These are potentially first in class specific Pim-1 inhibitors. SEL24 is currently in the lead optimization phase. First administration to humans is planned to take place in 2011.

CNS

Selvita also actively explores the area of psychiatric disorders, with a current focus on the schizophrenia and cognitive diseases. Currently, we have an active pre-clinical development project, on a selective antagonist of 5-HT₆ receptor – SEL73 – which is being developed for indications such as Alzheimer's disease or schizophrenia.

Introduction to medicinal chemistry capabilities

The primary goal of our Medicinal Chemistry Department is to discover and optimize novel compounds and identify best clinical development candidates for our internal programs. In addition we also offer medicinal chemistry expertise to our clients.

Selvita is partnering in a number of drug discovery projects providing support in the following areas:

- *Design of novel chemical entities using a combination of virtual screening of compound collections, and ligand- and structure-based drug design – quality lead compounds with high target potency, selectivity and drug-like properties are proposed for further development*
- *Hit validation and evaluation – hits from primary screen are synthesized and biological activity conformed in dose-response studies*
- *Hit explosion and lead generation guided by computer modeling*
- *Lead optimization for potency, selectivity, and ADMET properties*
- *SAR generation*
- *Patentability check*
- *Synthesis of lead compounds, advanced intermediates and reference compounds in multi-gram scale*

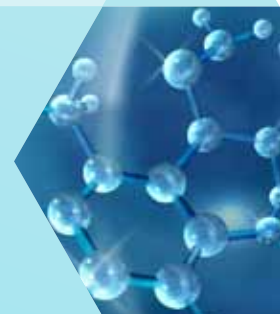
Selvita's Discovery Chemistry team consists of highly skilled and experienced professionals and operates in a newly opened facility. Our laboratory is designed for synthesis, purification and analysis, and equipped with top class equipment including Parr hydrogenation apparatus, flash purification systems, HPLC systems, lyophilizers, LC-MS, and LC-MS/MS. For virtual screening, computational drug design and ADME prediction, we use commercial software (GLIDE, Discovery Studio).

Pharmacology and Toxicology

Biological testing is an integral part of our drug discovery process. We routinely perform in-house determination of biological activity and pharmacological/toxicological profiling in a range of assays including:

IN VITRO CYTOTOXICITY ASSAYS – MTT, MTS, LDH, BRDU

In vitro evaluation of possible cytotoxicity of a drug candidate or its metabolites constitutes the first step in toxicological studies. MTT, MTS, LDH and BrdU assays provide a measure of the vitality of the cells, what follows, allow to assess the cytotoxicity of a tested substance.



CYTOMETRIC ANALYSIS OF APOPTOSIS AND NECROSIS (ANXV/PI STAINING)

Apoptosis is a physiological process of controlled cell death that is essential during embryonic development and in maintenance of tissue homeostasis. New drugs inducing apoptosis are expected to be very effective therapeutics for use in the treatment of cancer. Analysis of apoptosis/necrosis together with cell cycle arrest identification constitute excellent complement to cytotoxicity research.

CYTOMETRIC ANALYSIS OF CELL CYCLE INHIBITION (PI STAINING)

Studies of the proliferation characteristics of normal and malignant cells provide broad spectrum of information about molecular mechanisms of action of drugs and aid design of effective cancer therapy strategies.

ADME studies

Problems with absorption, distribution, metabolism and excretion (ADME) of promising drug candidate may lead to compound failure in clinical trials. To help to resolve these issues Selvita Group offers a comprehensive ADME platform supporting drug discovery projects from hit to preclinical candidate. Scope of our services includes:

SOLUBILITY TESTING

Solubility in aqueous media is one of the critical parameters which influences both pharmacokinetic and pharmacodynamic properties of chemicals. It also highly influences dissolution rate and bioavailability of the substance following oral administration, and therefore can alter the properties responsible for the in vivo performance.

PERMEABILITY ANALYSIS – PAMPA

The Parallel Artificial Membrane Permeability Assay (PAMPA) is the non-cell based assay for predicting passive absorption of drugs. Most drugs are absorbed through the intestines without using cellular pumps, therefore, passive permeability assays are useful for screening oral-absorption potential of drug candidates.

METABOLITE PROFILING

Administered drugs are subject to metabolism. Resultant metabolites might have pharmacological effect or even pose toxic risk on organism, it is therefore necessary to identify and evaluate them in terms of safety.

PLASMA BINDING

The pharmacokinetic and pharmacodynamic properties of drugs are largely a function of the binding of drugs to plasma proteins. High drug-protein binding can both reduce the amount of free drug available for target sites and prolong the duration of drug activity. For this reason it is crucial to estimate the percentage drug bound to plasma proteins.



CYP INHIBITION

The assays for cytochrome P450 inhibition facilitate the identification of drug candidates with lower potential for drug-drug interactions.

GENOTOXICITY TESTS

- Ames test (performed according to OECD TG 471 guideline)
- Micronucleus assay (performed according to OECD TG 487 guideline)

Custom synthesis and analytical chemistry support

In addition to facilitating the preclinical research mentioned, Selvita has a Contract Chemistry Department which specializes in following chemistry services:

- *planning and optimization of synthetic routes of organic substances,*
- *process optimization and scale-up,*
- *prediction of metabolic paths and substance toxicology profiles*
- *patent-literature search, including reviews of publications and patents regarding specific substances, substance classes and technologies*

Selvita also employs top class specialists in the field of physicochemical analysis and may provide a complex physicochemical characteristics of the synthesized substances. We are experienced in providing solutions for problems connected with the solid form of chemical compounds, such as:

- *characterisation and control of polymorphic form, development of a process to obtain a specific polymorphic form*
- *stability study and impurity profile of the active pharmaceutical ingredient (API)*
- *hygroscopicity and solubility studies.*

