

ChEMBL an Open Data Resource of Medicinal Chemistry and Patent Data

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The screenshot shows the ChEMBL homepage with the URL https://www.ebi.ac.uk/chembl/. The top navigation bar includes links for EBI, Wellcome Trust, and various social media and citation platforms. The main content area features a search bar with tabs for Compounds, Targets, Assays, and Documents, along with an "Activity Source Filter". Below the search is a "Ligand Search" section with a chemical editor interface. A central feature is the "List Search" where users can enter SMILES or ChEMBL IDs. To the right is a "Biologicals Blast Search" input field. On the left, there's a sidebar with "ChEMBL Statistics" (e.g., 17 million compounds, 9,356 targets), a "ChEMBL Blog" section, and a "Substructure Search" tool.

This screenshot displays a table of drug targets from the ChEMBL database. The columns include Molecule Type, First Approval, ATC Code, USAN Stem, Mechanism of Action, Target Name, Action Type, Organism, Target Type, Binding Site Name, and Mechanism Refs. The table lists several targets, such as Alogliptin, -rafenib, Dabrafenib, Dimethyl Fumarate, and Glycerol Phenylbutyrate, each with its respective chemical structure and detailed biological information.

Molecule	Type	First Approval	ATC Code	USAN Stem	Mechanism of Action	Target Name	Action Type	Organism	Target Type	Binding Site Name	Mechanism Refs
	Small molecule	2013	A10BH04	-gliptin	Dipeptidyl peptidase IV inhibitor	Dipeptidyl peptidase IV	INHIBITOR	Homo sapiens	SINGLE PROTEIN		DailyMed
	Small molecule	2013		-rafenib	Serine/threonine-protein kinase B-raf inhibitor	Serine/threonine-protein kinase B-raf	INHIBITOR	Homo sapiens	SINGLE PROTEIN		DailyMed
	Small molecule	2013			Kelch-like ECH-associated protein 1 inhibitor	Kelch-like ECH-associated protein 1	INHIBITOR	Homo sapiens	SINGLE PROTEIN		DailyMed PubMed PubMed
	Small molecule	2013			Glutamine chelating agent	Glutamine	CHELATING AGENT	Homo sapiens	SMALL MOLECULE		DailyMed
	Small molecule	2013	A16AX09								
	Oligonucleotide	2013	C10AX11	-rsen	Apo-B 100 mRNA antisense inhibitor	Apo-B 100 mRNA	ANTISENSE INHIBITOR	Homo sapiens	NUCLEIC ACID		DailyMed

ChEMBL

- The world's largest primary public database of medicinal chemistry data
 - ~1.4 million compounds, ~9,000 targets, ~12 million bioactivities
- Truly Open Data - CC-BY-SA license
- Many download/access formats
 - Semantic Web
 - RDF download, SPARQL endpoint at <http://rdf.ebi.ac.uk/chembl>
 - ChEMBL Applications
 - myChEMBL – linux VM
 - ChEMpi – raspberry pi
- ChEMBL 18 released next week

The screenshot shows the SureChem website interface. At the top, there's a navigation bar with links like 'Home', 'Products', 'Support', 'Contact', 'Blog', 'Sign Up', and 'Log In'. Below the header, a banner reads 'Patent chemistry made easy and accessible' with the subtext 'We're integrating patent chemistry into the scientific community and giving customers control over data'. There are two buttons: 'SIGN UP FREE' (takes just 30 seconds) and 'TAKE THE TOUR' (see all SureChem products). The main area is titled 'Search Results' and shows a query for a specific chemical structure. The structure is a tricyclic compound with hydroxyl groups. Below the structure, its name is listed: '(1R,6S,10S,11R)-4-methyl-12-oxo-1,2-dihydro-3H,11H-dibenzo[1,2-e:4,5-e']dioxepin-10,11-diol'. It also shows its molecular weight (265.358), SMILES string, and a 'View chemical page' link. To the right, there are options to 'View results as: Matrix | Table'. Below this, there's a 'Search' section where users can draw or paste a chemical structure to perform exact, similarity, and substructure searches. It includes fields for keyword, patent bibliographic field, command line, and a 'Combine all of them with structure search' button. At the bottom, there are links for 'Search', 'View', and 'Link', each with a 'View more' link. A large green button at the bottom encourages users to 'See our products, sign up or get in touch'.

SureChEMBL

- EMBL-EBI have acquired the SureChem product from Digital Science
 - >15 million chemical structures
 - Automatically extracted chemical structures from full-text patent
- EMBL-EBI will Provide an ongoing free, Open resource to entire community
 - Add target, sequence, disease, animal model, cell-line indexing

Document Similarity

Document 1

2432

J. Med. Chem. 2002, 45, 2432–2453

Design of Selective Thrombin Inhibitors Based on the (R)-Phe-Pro-Arg Sequence

John C. Daniiewicz,^{1,2} Stuart M. Abel,¹ Alan D. Brown,² Paul V. Fish,^{3,4} Edward Hawkeswood,⁵ Stephen J. Holland,⁶ Keith James,² Andrew B. McElroy,⁷ John Overington,⁸ Michael J. Powling,⁹ and David J. Rance¹

Departments of Discovery Chemistry, Drug Metabolism, Discovery Biology, and Molecular Informatics Structure and Design, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, United Kingdom

Received December 21, 2001

Potent and selective inhibitors of thrombin were sought based on the (R)-Phe-Pro-Arg sequence. The objective was to generate similar binding interactions to those achieved by potent competitive inhibitors of the argatroban type, so eliminating the need for covalent interaction with the catalytic serine function, as utilized by aldehyde and boronic acid type inhibitors. Improving the S_1 substrate interaction by substitution of arginine with a 4-alkoxybenzamidine residue resulted in a lead ($D = 0.3 \mu\text{M}$). The hydrogen bond to the His residue at the active site is lost, modeling indicating that a new H-bond is generated between the alkoxy oxygen atom and the catalytic Ser-195 hydroxyl group. Substitution of the benzamidine system by 1-pyridinylpyridine then gave compounds that provided a further gain in selectivity over trypsin. Importantly, these compounds had shown that these compounds were likely to be lipophilic ($\log D = 0.4$ and $+0.2$, respectively) and to suffer rapid hepatic extraction, presumably via biliary elimination. Accordingly, both proved short-acting when administered intravenously to rats and showed poor activity when given intraduodenally. The aim was then to reduce polarity without losing $\log D < 1.2$, which would be required for oral bioavailability in preventing rapid clearance. It was anticipated that compounds of this type would rely on the selection of paracellular route of absorption from the gastrointestinal tract. Potent polar analogues with selectivity > 1000 over trypsin were obtained. The best in vivo activity was shown by compound 12, having an oral bioavailability of 10% and a $t_{1/2} = 10$ h. These data are relative to analogues with similar physicochemical properties derived from argatroban, consistent with the hypothesis that molecular shape is an additional important determinant of paracellular absorption.

Introduction

The search for potent selective and orally active thrombin inhibitors has gathered momentum in recent years.¹ Thrombin is the last in a cascade of trypsin-like protease serine proteases, catalyzing the conversion of fibrinogen to fibrin, activation of FXIII and inducing platelet aggregation is a key enzyme in both argatroban and napsagatran. Unfortunately, most of these compounds is orally inactive due to either poor absorption from the gastrointestinal tract and/or rapid clearance via the bile.^{2,3}

A second inhibitor type is based on the substrate irreversibly cleaved by the kinase PPACK and includes compounds such as Dal-716⁴ and eptegran (GYKI-14 766).⁵ These compounds interact covalently with the hydroxyl group of the catalytic serine residue. The neighbor proline ring and (R)-Phe side chain can be used to fill the S₁ and S₂ sites in a fashion as the two distal lipophilic groups of the first series.⁶ Though oral activity has been claimed for these compounds, we were concerned that high enzyme selectivity may be unreliable when solubility and affinity is derived by interacting covalently with the ubiquitous active site serine function. In the case of aldehyde type inhibitors, there is also the potential problem of achieving adequate optical and chemical stability.

10.1021/jm0111334 CCC: \$22.00
Published on Web 05/1/2002

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[†] Senior author.

[‡] Department of Discovery Chemistry.

[§] Department of Drug Metabolism.

[¶] Department of Discovery Biology.

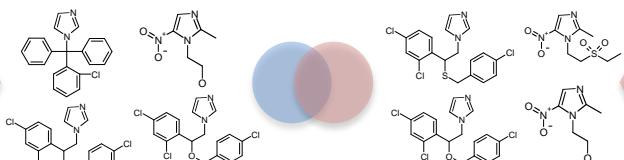
^{||} Molecular Informatics Structure and Design.

Words, n-grams, ...

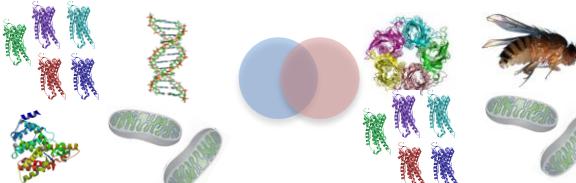
toxicity
synthetized
thrombin
pyridine
cancer

pharmacokinetics
toxicity
pyridine
trypsin
ulcerative colitis

Chemicals



Targets



Document 2

2432

J. Med. Chem. 2002, 45, 2432–2453

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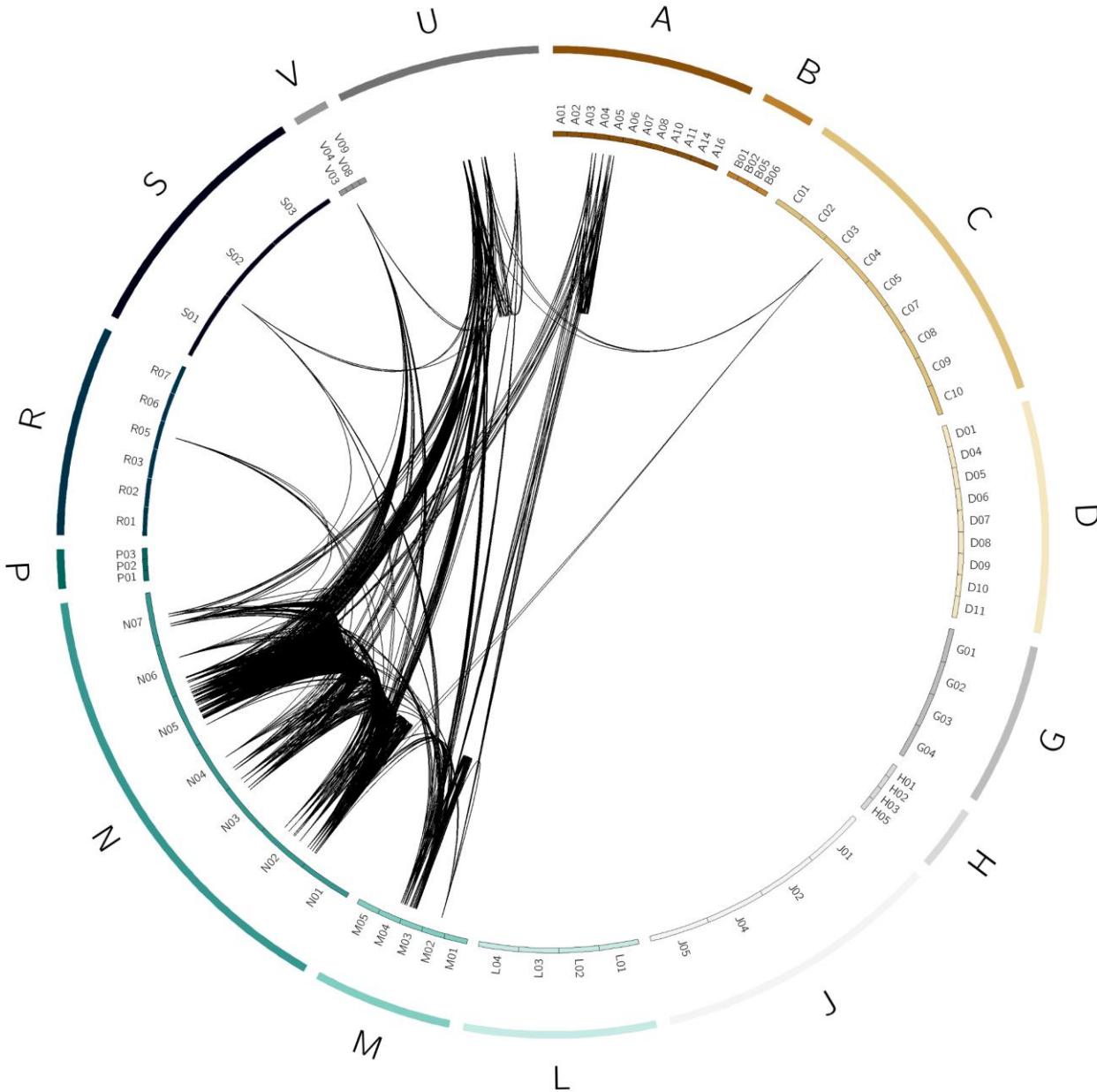
basic P₁ side chain pack together to interact with the hydrophobic S₁ site.⁷ Napsagatran (Ro 46 6240), developed by Hilpert et al.,⁸ though having a more complex side chain profile, can nevertheless be viewed as belonging to this group. The main interaction with the catalytic serine residue is via a hydrogen bond to the carboxylate function in both argatroban and napsagatran. Unfortunately, most of these compounds is orally inactive due to either poor absorption from the gastrointestinal tract and/or rapid clearance via the bile.^{2,3}

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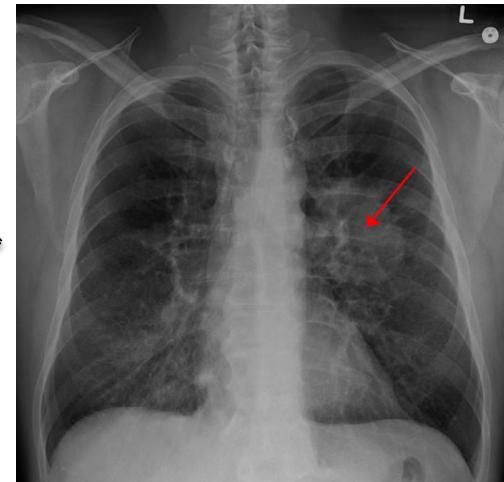
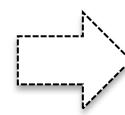
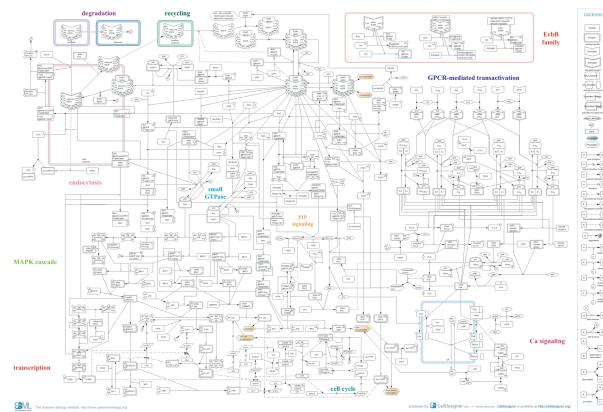
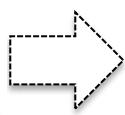
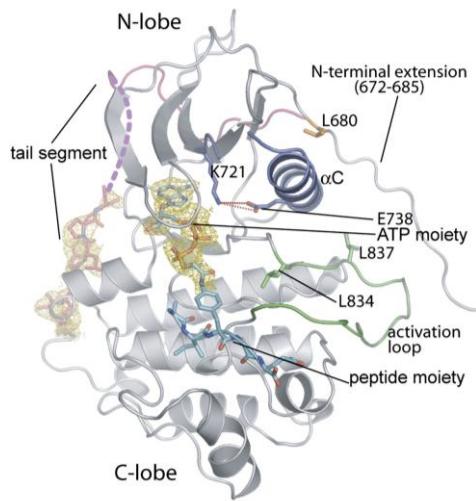
- Document similarity methods currently rely on word/concept co-occurrence
- Possible to extend to include overlap/similarity of shared molecular objects
 - Sequences and Ligands
 - Greater richness possible in similarity measures and searches
 - Sequences – Sequence similarity, domains, structures,...
 - Ligands – Tanimoto similarity, scaffolds,....

Polypharmacology via Binding Sites



ATC Disease
indications linked
by shared
similarity of
target site, for
Ligand-gated ion
channels (Pfam
PF02932)

Target – Pathway - Disease



Assays in Drug Discovery



Human
clinical trial

- Traditional medicines
 - Aspirin, Artemesinin, Arsenic trioxide....
 - Very slow and error prone
 - Not hypothesis led, *ad hoc* discovery

Assays in Drug Discovery



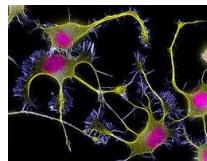
Animal
disease model



Human
clinical trial

- +ve
 - Higher Throughput
 - Greater Safety
 - Faster, cheaper, smaller scale
- -ve
 - Less predictive

Assays in Drug Discovery



Functional
assay



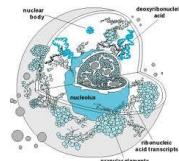
Animal
disease model



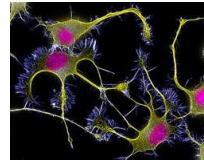
Human
clinical trial

- +ve
 - Higher Throughput
 - Mechanistic insights and use of advances in basic science
 - Faster, cheaper, smaller scale
- -ve
 - Less predictive

Assays in Drug Discovery



Cell-based screen



Functional assay



Animal disease model

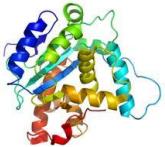


Human clinical trial

- +ve
 - Higher Throughput
 - Mechanistic insights and use of advances in science
 - Faster, cheaper, smaller scale
- -ve
 - Less predictive

Assays in Drug Discovery

1980s



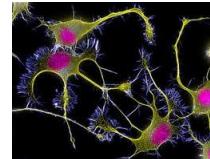
Biochemical assay

1960s



Cell-based screen

1950s



Functional assay

1920s



Animal disease model

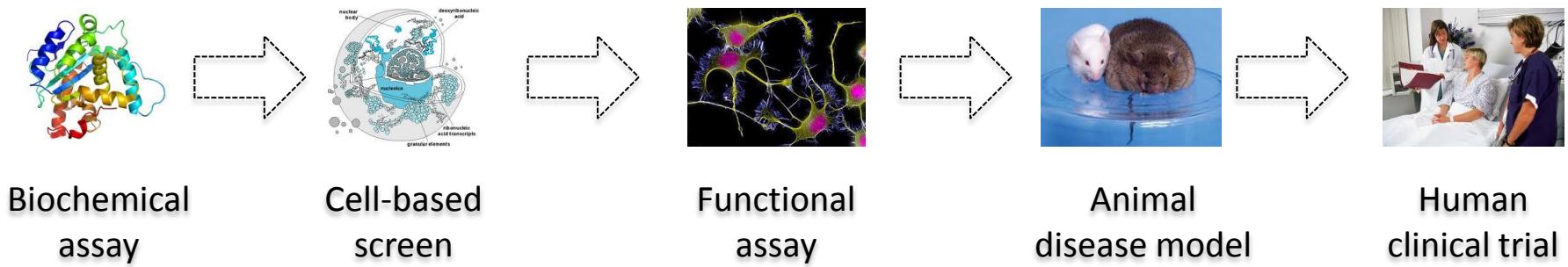
Ancient



Human clinical trial

- +ve
 - Higher Throughput
 - Mechanistic insights and use of advances in science
 - Recombinant DNA technology and Genomics
 - Faster, cheaper, smaller scale
- -ve
 - Less predictive

Drug Discovery Assay “Cascade”



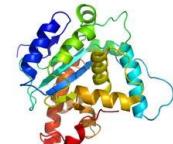
- Move from '*quick, low-cost, less predictive*' assays to '*slow, high-cost, more predictive*' assays
- Make selection of which compounds to progress to later assays on basis of activity in earlier screens
 - Early, cheap assays are used a lot of times; later, expensive assays rarely
 - Attrition – failure of compounds in that screening pipeline
 - Clinical trials configured in staged Phase 1, 2, 3 mode

Assay Costs

Costs are estimates!!



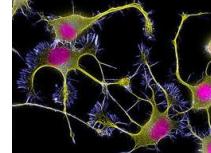
In silico



Biochemical
assay



Cell-based
screen



Functional
assay



Animal
disease model



Human
clinical trial

Cost (€) 0.0001

10

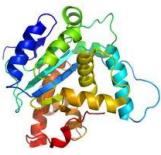
100

1,000

10,000

100,000,000

Targets & Diseases Connected via Drugs



Biochemical
assay



Cell-based
screen



Functional
assay



Animal
disease
model



Human
clinical trial

PPAR γ

PPAR α

SUR1

K(ATP) channels

DPP-IV

GLP1R

Thrombin

Factor Xa

Target

.....

Type 2 diabetes

.....

.....

.....

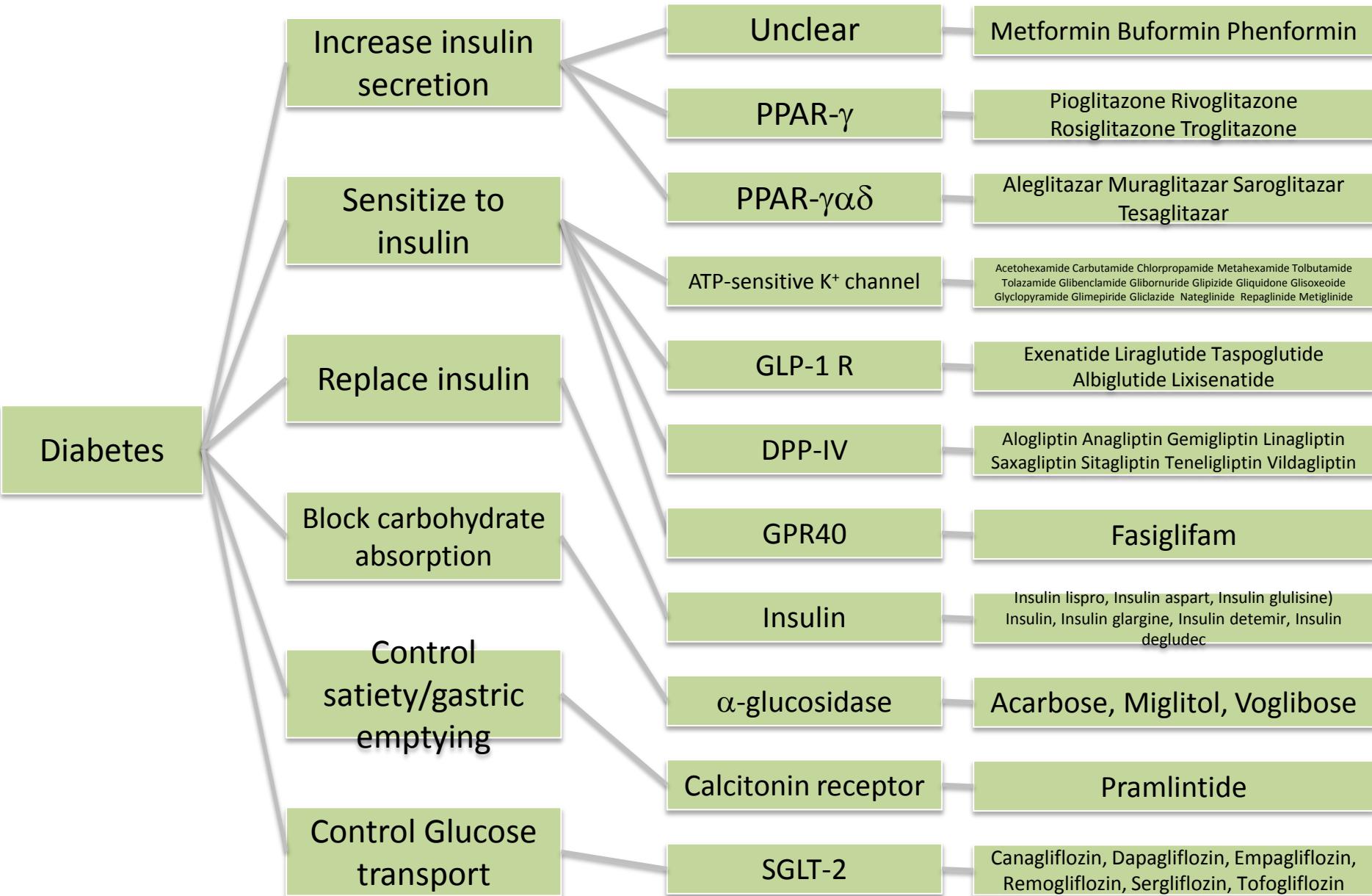
.....

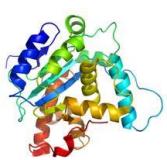
Deep vein thrombosis

.....

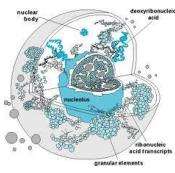
Disease

Ontology of Diabetes Drugs

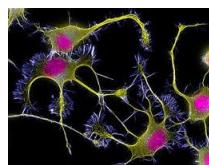




Biochemical
assay



Cell-based
screen



Functional
assay



Animal
disease model



Human
clinical trial

Target Assay

Cellular Assay

Genetic/Induced Animal Model

Clinical Trial

PPAR-g

PPAR-a

PPAR-d

PTP1B

DPP-IV

RXR-a

SGLT-2

Fructose-1,6-bisphosphatase

Acyl-CoA desaturase

FXR

SGLT-1

Glucose-6-phosphatase

G-protein bile acid receptor 1

NOD mouse

Ob/Ob mouse

db/db mouse

KK mouse

Nagoya-Shibata-Yasuda
(NSY) mouseStreptozocin-treated
mouse

Alloxan-treated mouse

BB rat

Zucker fa/fa rat

Goto Kakizaki (GK) rat

Otsuka Long-Evans
Tokushima fatty (OLETF) rat

Streptozocin-treated rat

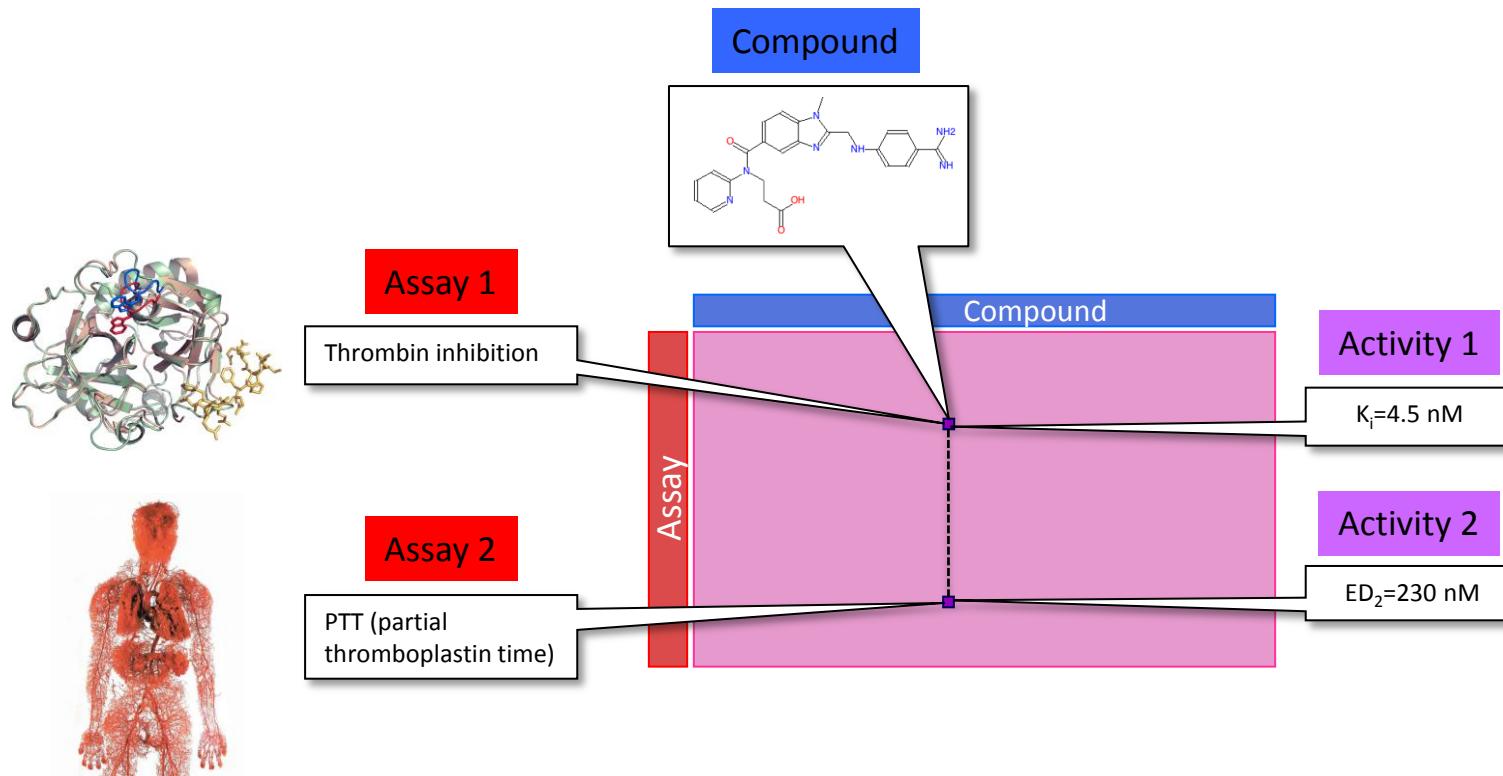
Alloxan-treated rat

Psammomys obesus

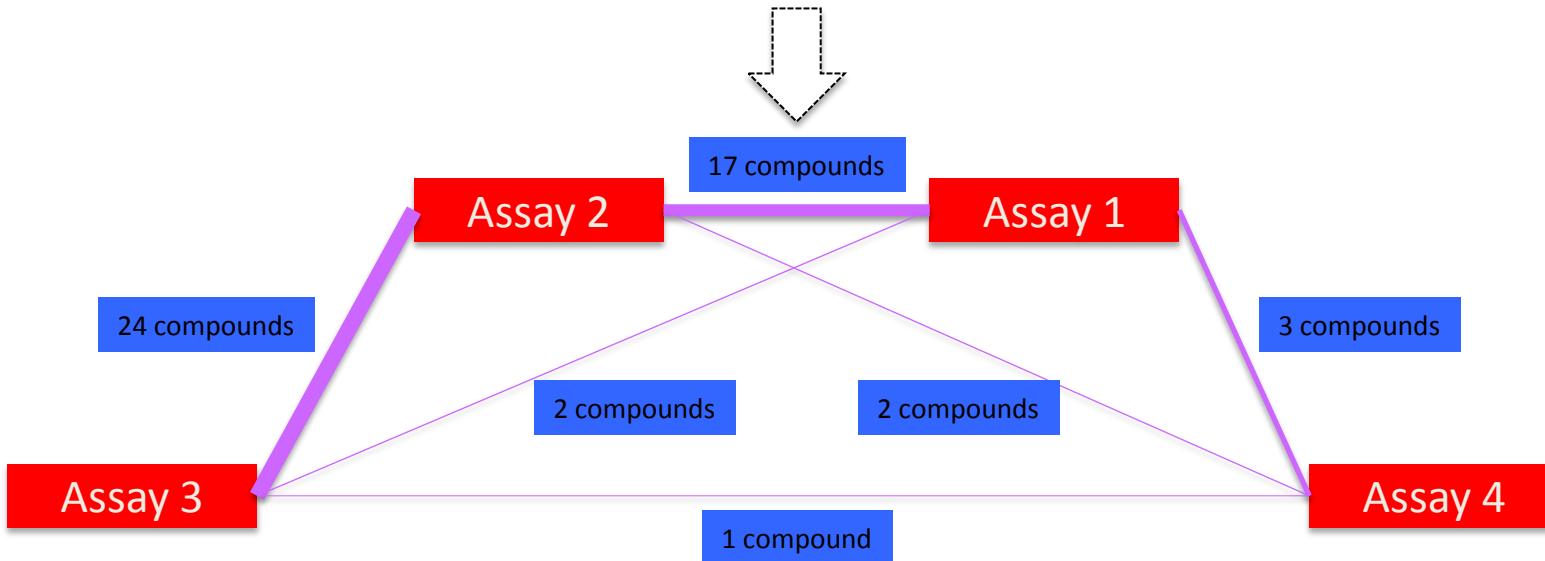
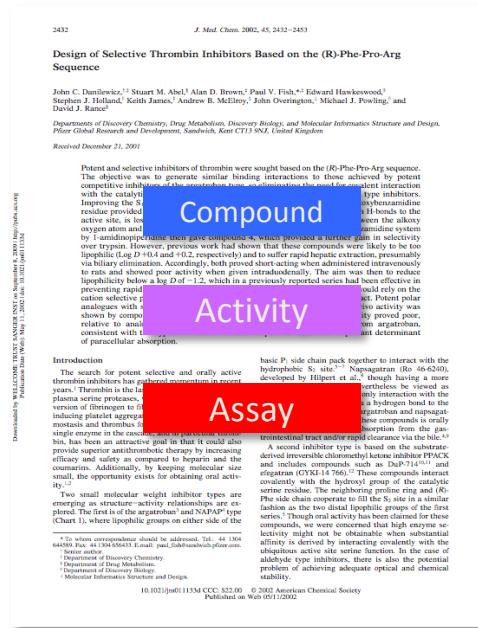
Alloxan-treated dog

Type 1 diabetes
(E10)Type 2 diabetes
(E11)Gestational
diabetes (O24)CF-related
diabetesGlucocorticoid-
related diabetesMaturity onset-diabetes
of the young - MODY 2iPSC derived β -cells
(GCK mutant)

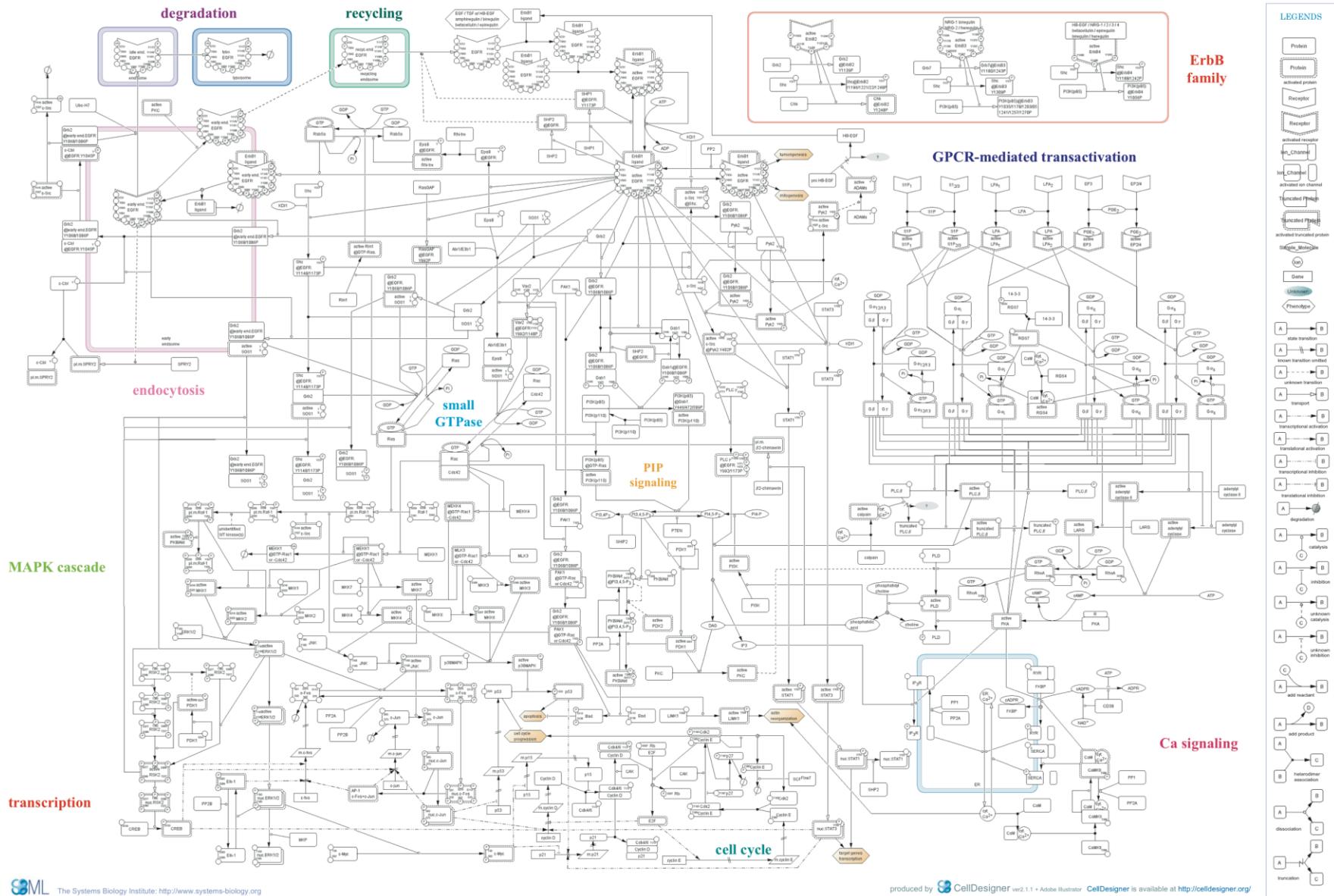
Compounds & Bioassays in ChEMBL



ChEMBL Assays as a Graph

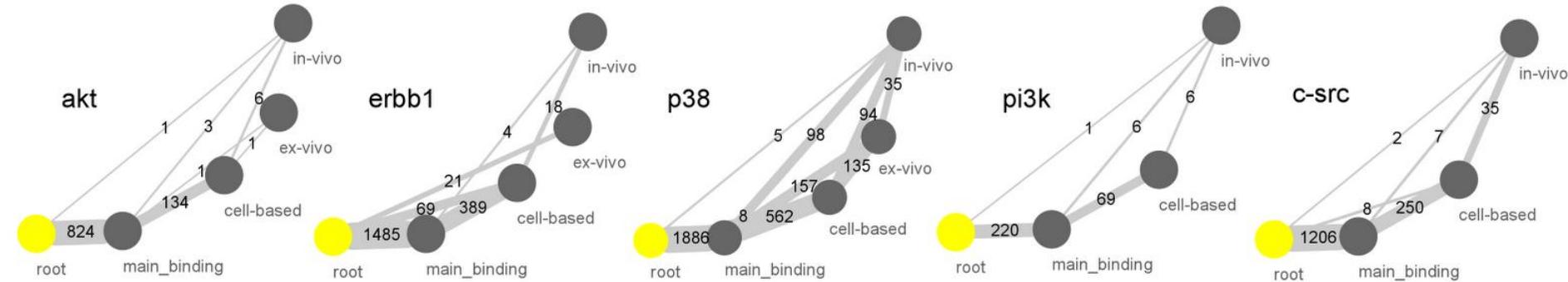


EGFR Signaling Pathway



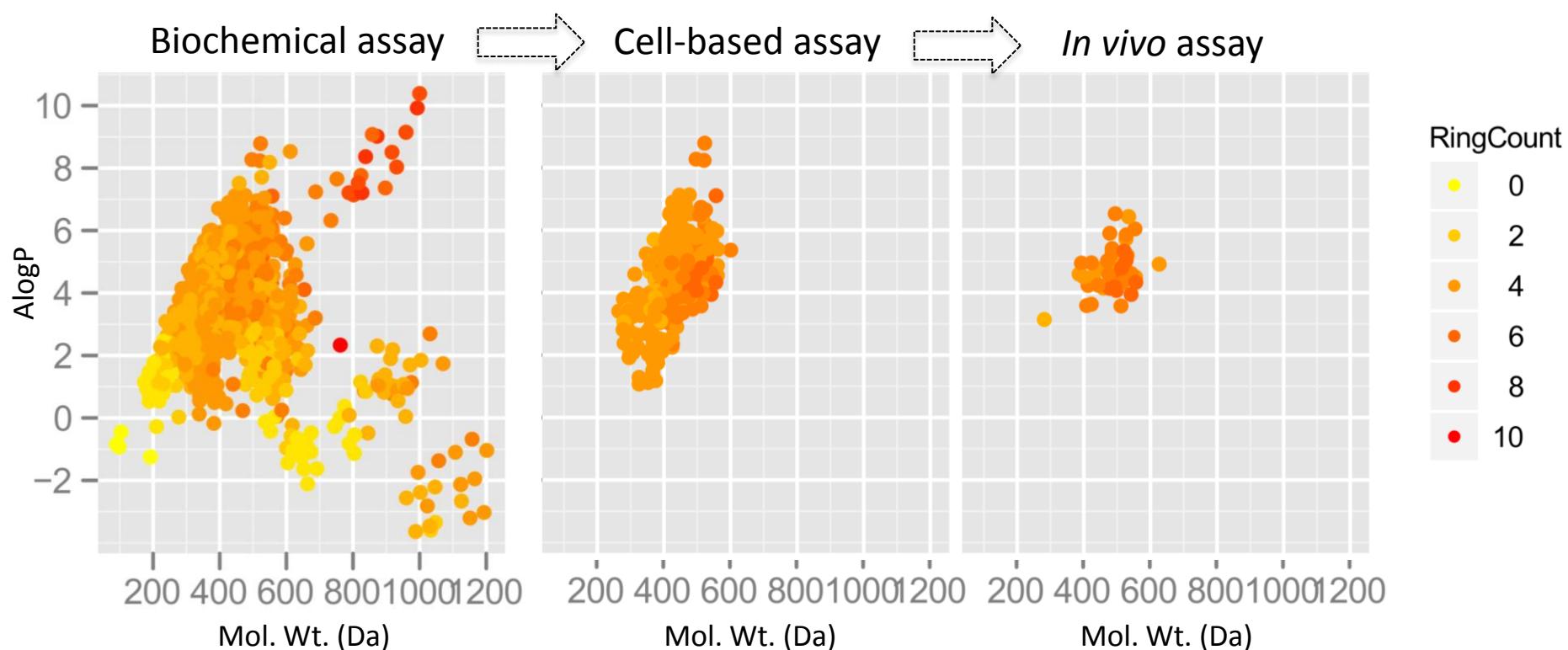
EGFR Assay Cascades From ChEMBL

Assay Network for EGFR pathway inhibitors



EGFR Assay Cascades from ChEMBL

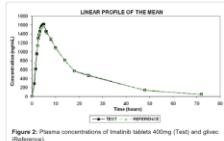
Physicochemical properties for cSrc EGFR pathway inhibitors



Extraction & Curation of PK Data

Single Imatinib 400 mg dose

Citation: Jashari D, AlSwihi M, Ghannam M (2011) Bioavailability of a New Generic Formulation of Imatinib Methylate 400mg Tablets Versus Glivec in Healthy Male Adult Volunteers. J Bioequavil Availab 3: 161-164. doi:10.4172/jba.1000077



within 80% to 125% FDA acceptance range for generic drugs which indicated that Imatinib tablets 400mg and Glivec tablets 40mg are bioequivalent under fed conditions. The pharmacokinetics of the imatinib tablets and the capsules and tablets subjects were well tolerated to Imatinib and no major side-effects were observed.

Conclusion

Based on statistical results, it can be concluded that both products tested in this study comply with regulatory requirements to be considered bioequivalent. Therefore, the two products can be considered interchangeable with the reference based on their biopharmaceutical performance. Both products were well tolerated and safe in healthy volunteers, and that both products can be considered equally effective and interchangeable in medical practice based on the pharmacokinetic effect.

Acknowledgment

The authors are grateful to Hikma Pharmaceuticals Plc, which is the sponsor of the bioequivalence study for Imatinib 400 mg tablets. The authors wish to acknowledge the support of the pharmaceuticals Research and development department of the National Research Center (NRC), Egypt. The authors also thank Dr. Farid Taha, Head of Clinical Pharmacology Department, National Research Center, DRUGS, URUGUAY for critical review. Many thanks to Dr. Ayman Abtesi for his review.

References

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User friendly online submission system makes your workflow easier and faster

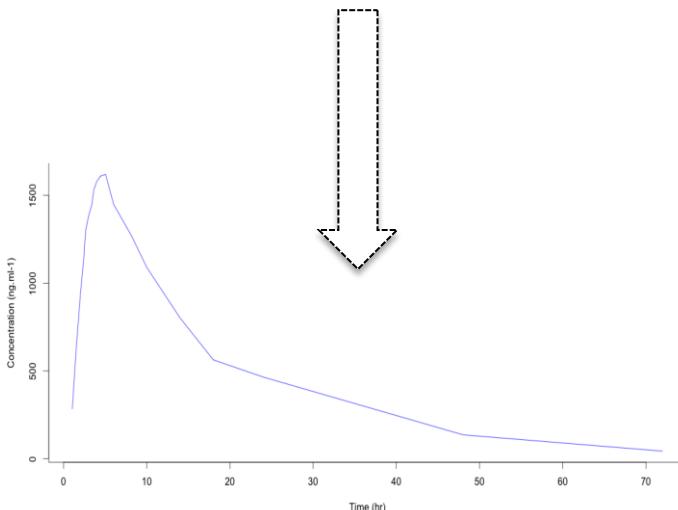
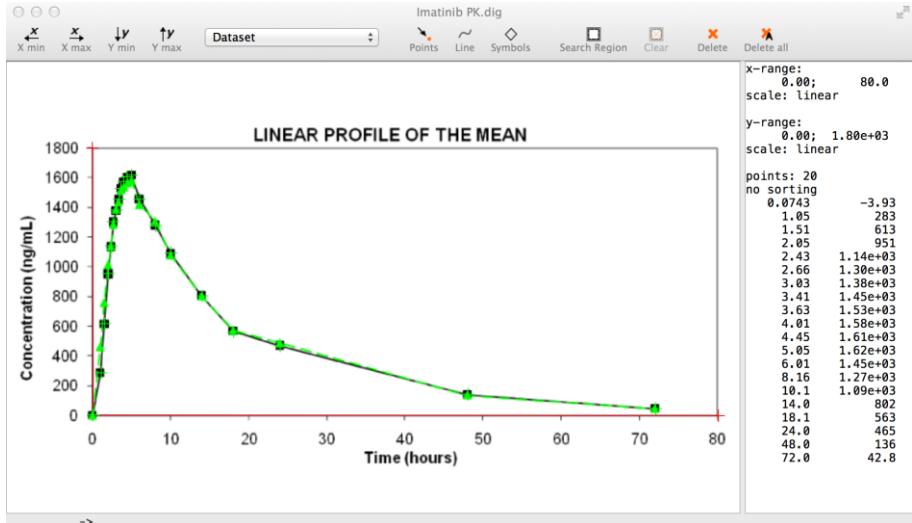
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Bioequivalence & Bioavailability

Research Article

Bioavailability of a New Generic Formulation Tablets Versus Glivec in Healthy Male Ad

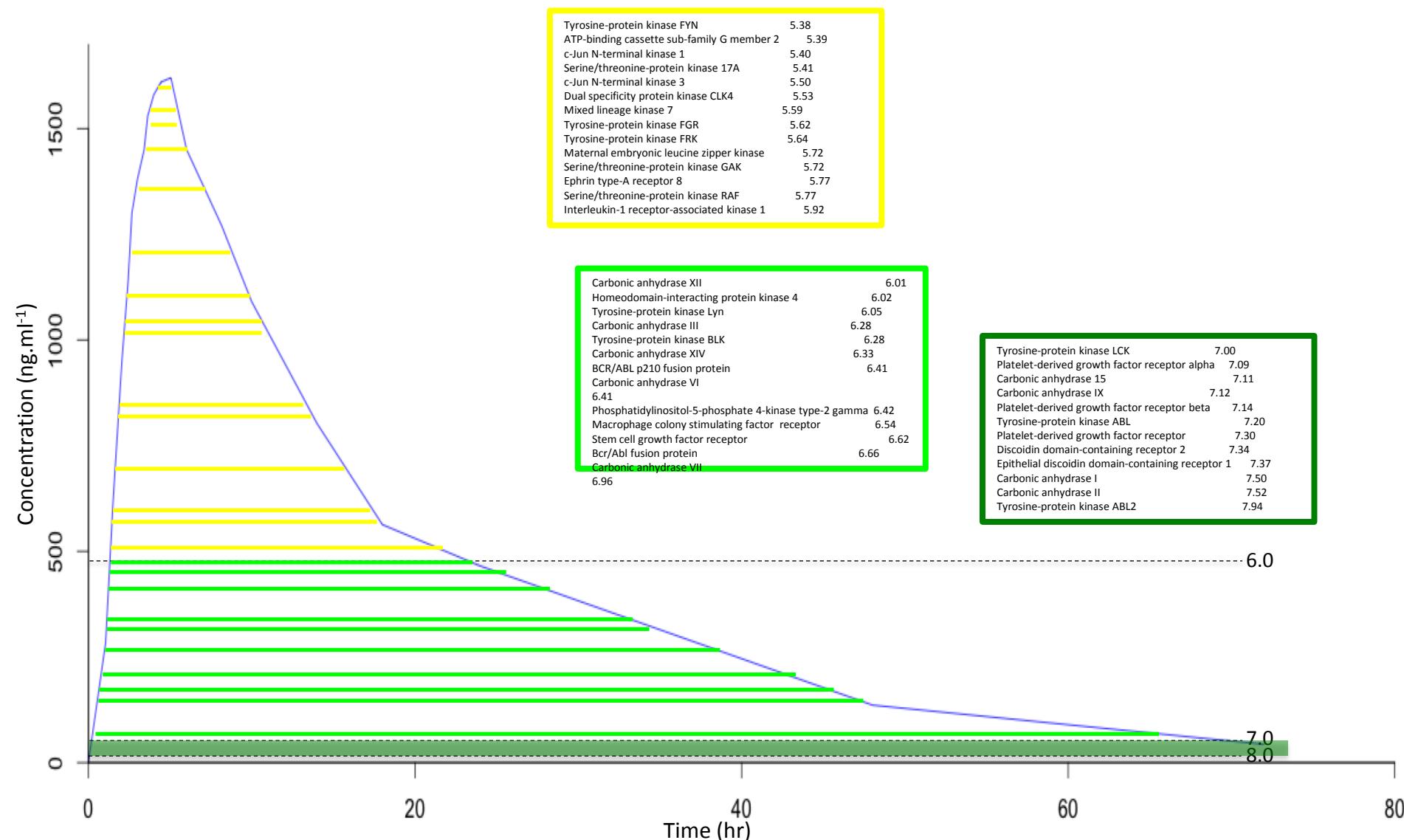
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ESCI Pharmacy, Jordan

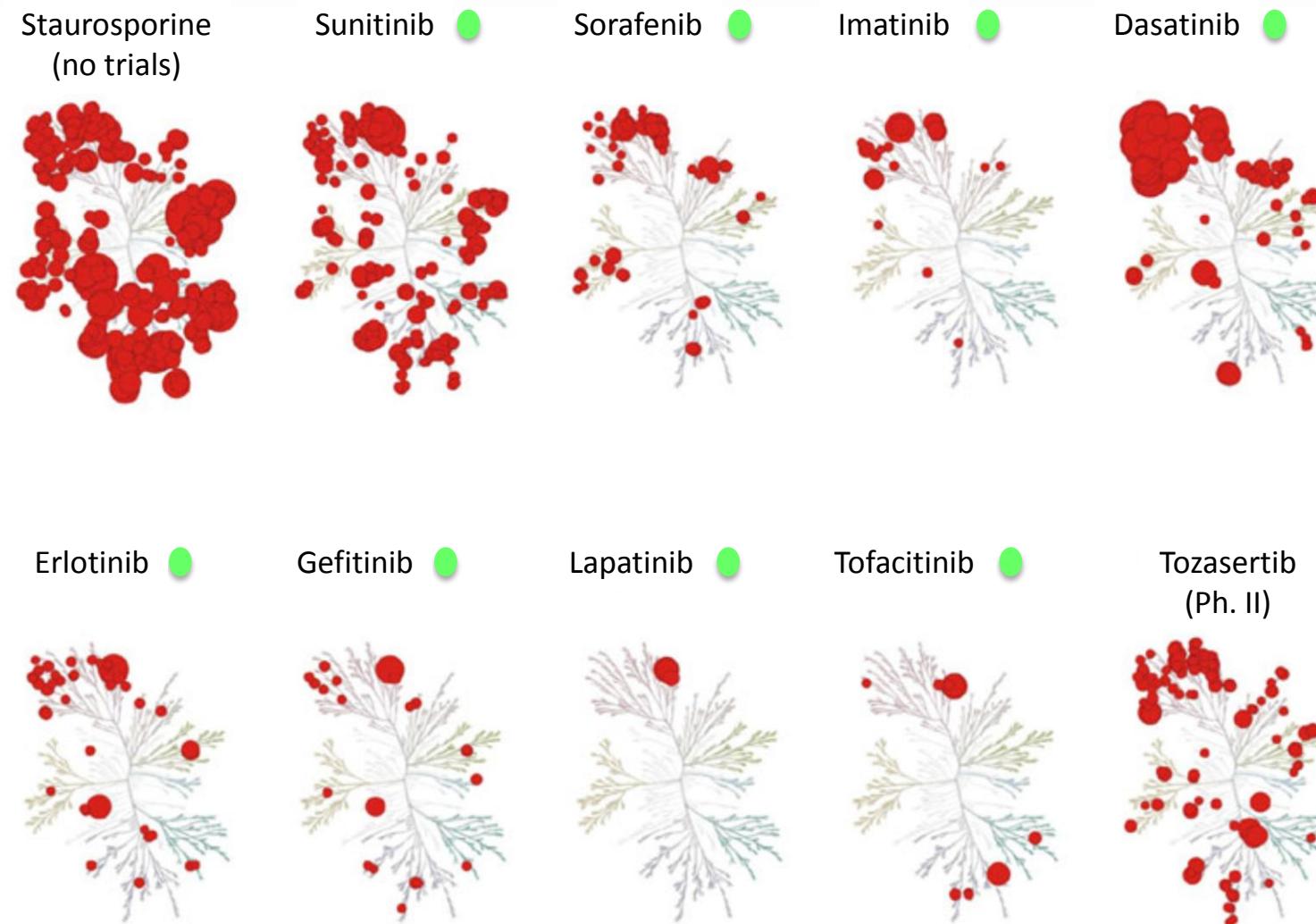
Abstract

Imatinib is a highly selective inhibitor of tyrosine kinase (TK) and the cost of the drug is prohibitive especially in the development of pharmacokinetic profile of a new generic formulation. Imatinib is a tyrosine kinase inhibitor used in the treatment of chronic lymphocytic leukaemia in healthy male volunteers (fed state). The study was single c-periodic oral administration. The pharmacokinetic study was performed (parallel design) in accordance with Good Clinical Practice (GCP) (e.g. non-*ex-smokers, of at least 18 years of age but not older than 50 years, body mass index between 18.5 and 24.9 kg/m², non-smokers, non-drinkers, non-*ex-smokers, of at least 18 calendar days. Under drug and *et al.,* patients were excluded if they had any history of disease or symptoms after the collection of the last blood sample of the study. Safety was evaluated through the assessment of adverse events, and laboratory tests. Imatinib plasma samples were analyzed employing a validated method using LC/MS/MS. For the bioequivalence study, the mean (± SD) AUC₀₋₂₄, 0-100, 0-120, 0-200, 0-300, 0-400, 0-500, 0-600, 0-700, 0-800, 0-900, 0-1000, 0-1100, 0-1200, 0-1300, 0-1400, 0-1500, 0-1600, 0-1700, 0-1800, 0-1900, 0-2000, 0-2100, 0-2200, 0-2300, 0-2400, 0-2500, 0-2600, 0-2700, 0-2800, 0-2900, 0-3000, 0-3100, 0-3200, 0-3300, 0-3400, 0-3500, 0-3600, 0-3700, 0-3800, 0-3900, 0-4000, 0-4100, 0-4200, 0-4300, 0-4400, 0-4500, 0-4600, 0-4700, 0-4800, 0-4900, 0-5000, 0-5100, 0-5200, 0-5300, 0-5400, 0-5500, 0-5600, 0-5700, 0-5800, 0-5900, 0-6000, 0-6100, 0-6200, 0-6300, 0-6400, 0-6500, 0-6600, 0-6700, 0-6800, 0-6900, 0-7000, 0-7100, 0-7200, 0-7300, 0-7400, 0-7500, 0-7600, 0-7700, 0-7800, 0-7900, 0-8000, 0-8100, 0-8200, 0-8300, 0-8400, 0-8500, 0-8600, 0-8700, 0-8800, 0-8900, 0-9000, 0-9100, 0-9200, 0-9300, 0-9400, 0-9500, 0-9600, 0-9700, 0-9800, 0-9900, 0-10000, 0-10100, 0-10200, 0-10300, 0-10400, 0-10500, 0-10600, 0-10700, 0-10800, 0-10900, 0-11000, 0-11100, 0-11200, 0-11300, 0-11400, 0-11500, 0-11600, 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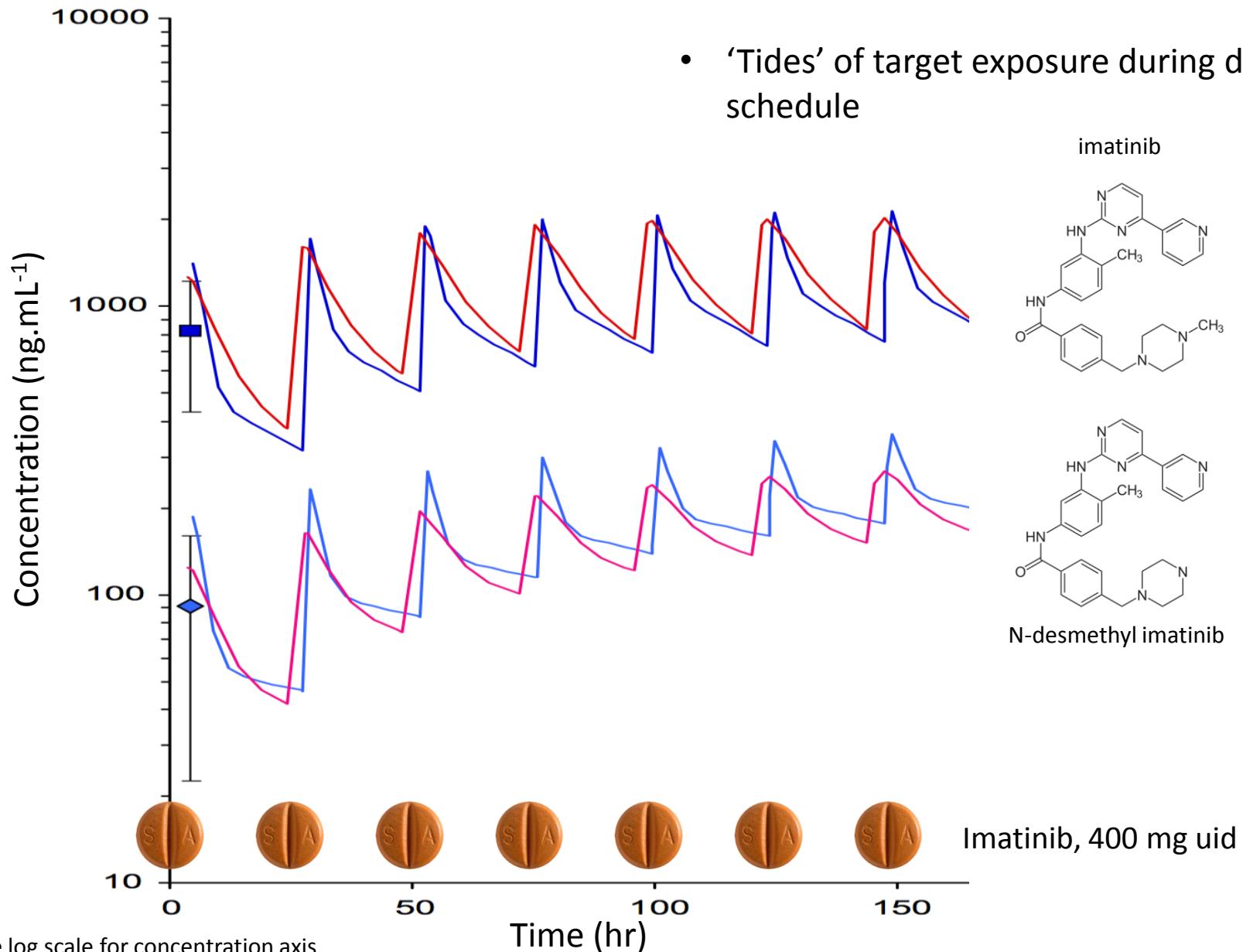
Imatinib Polypharmacology Spectra



Kinase Inhibitor Polypharmacology



Imatinib Pharmacokinetics



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