
Scientific contributions
The Challenges
Prospects
Drug discovery for Eumycetoma
Objective
Results
Methodology

Design and synthesis of a novel series of imidazo[1,2-b]pyridazines as antifungals against *Madurella mycetomatis*

Lamis Y.M Elkheir

Research Assistant, Mycetoma Research Center

Lecturer, Dep. of pharmaceutical chemistry, Faculty of Pharmacy, UofK.

Co-Director and Training Lead, African Reproducibility Network (AREN)

Professor Ahmed Hassan Fahal
MBBS, FRCS, FRCSI, FRCS(G), MD, MS, FRCP (London), FRCPath.
Professor of Surgery, University of Khartoum, Khartoum, Sudan.

Professor Magdi Awadalla
Professor of Pharmaceutical Chemistry, faculty of Pharmacy, University of Khartoum

université de TOURS

Simba EA 7502

Transplantation Immunologie Inflammation T2i

Prof. Cécile Enguehard-Gueiffier
Professor of medicinal chemistry, university of tours, France

Dr Pierre-Olivier Delaye
Associate professor of medicinal chemistry, university of tours, France

Dr. Sebastian Roger
Associate professor of Physiology , university of tours, France

Dr. Pierre Bisson
Associate professor of Physiology
university of tours, France

Erasmus MC

Dr. Wendy van de Sande
Associate professor of Microbiology & Infectious Diseases,
Erasmus MC, the Netherlands


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Eumycetoma

Mycetoma

What is Mycetoma?

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- Caused by **Bacteria** (Actinomycetoma) or **Fungi** (Eumycetoma)

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- It most commonly affects the feet (Madura foot).
- Caused by **Bacteria** (Actinomycetoma) or **Fungi** (Eumycetoma)
- It is the **diseases of the poor**, mainly affecting farmers and herdsmen in rural areas.

Geographical Distribution (Mycetoma Belt)

Geographical Distribution (Mycetoma Belt)

Tropical and subtropical environment

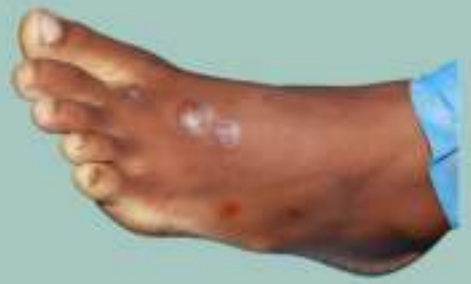
Disease Progression

Disease Progression

Microorganism
in thorns???

Disease Progression

Microorganism
in thorns???

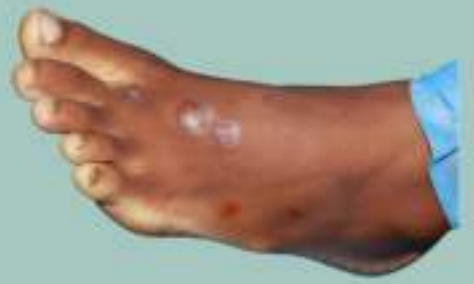


Small nodule

Disease Progression

Microorganism in thorns???

Time??



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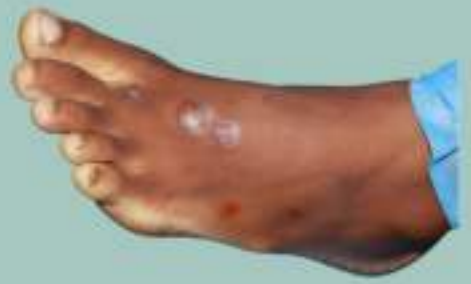

Small nodule

Oozing sores

Disease Progression

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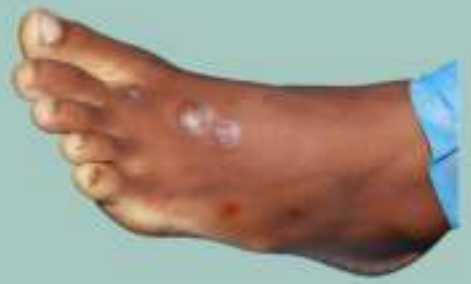

Small nodule

Grains

Oozing sores

Disease Progression

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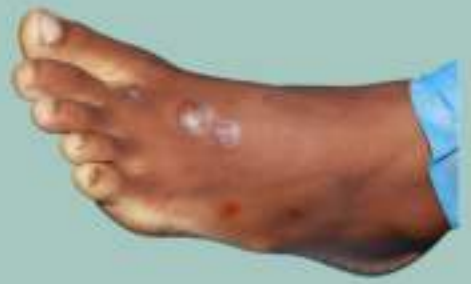
in thorns???

Time??



Small nodule

Grains

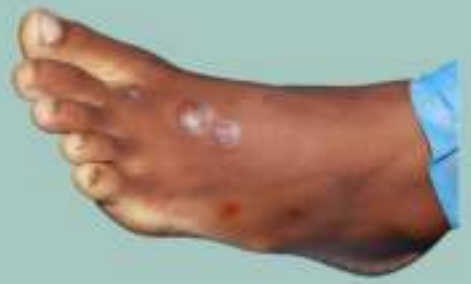
Oozing sores

Spread of infection to involve skin,
muscles, and bone

Disease Progression

Microorganism in thorns???

Time??



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Grains

Oozing sores

Disfigurement

Spread of infection to involve skin, muscles, and bone

Disease Progression

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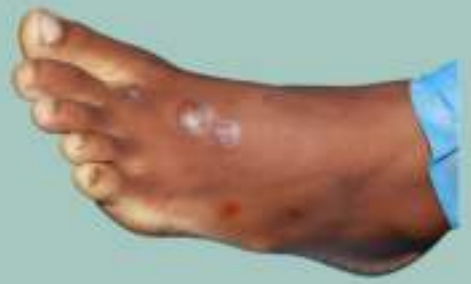

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Grains

Oozing sores

Disfigurement

Disabilities

Spread of infection to involve skin,
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Disease Progression

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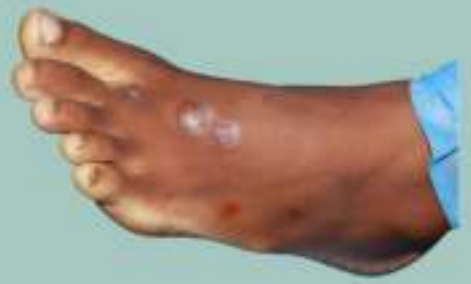

Small nodule

Grains

Oozing sores

Disfigurement

Disabilities

Social stigma

Spread of infection to involve skin,
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Disease Progression

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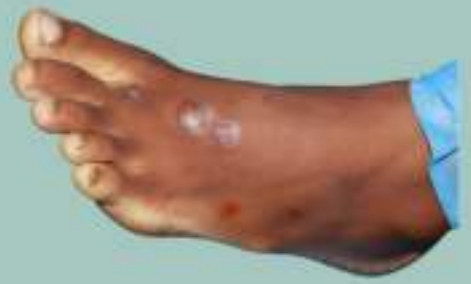

Small nodule

Grains

Oozing sores

Disfigurement

Disabilities

Social stigma

Death

Spread of infection to involve skin,
muscles, and bone

reas.

Tropical and subtropical environment

reas.

Tropical and subtropical environment

Treatment of Mycetoma

reas.

Tropical and subtropical environment

Treatment of Mycetoma

Actinomycetoma

Eumycetoma

reas.

Tropical and subtropical environment

Treatment of Mycetoma

Actinomycetoma

Antibiotics.
Few months of treatment.
90% cure rate.
Low recurrence rate

Eumycetoma

reas.

Tropical and subtropical environment

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Antifungals (azoles) + Surgery (excision or amputation)
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reas.

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Immense need for finding NOVEL drugs


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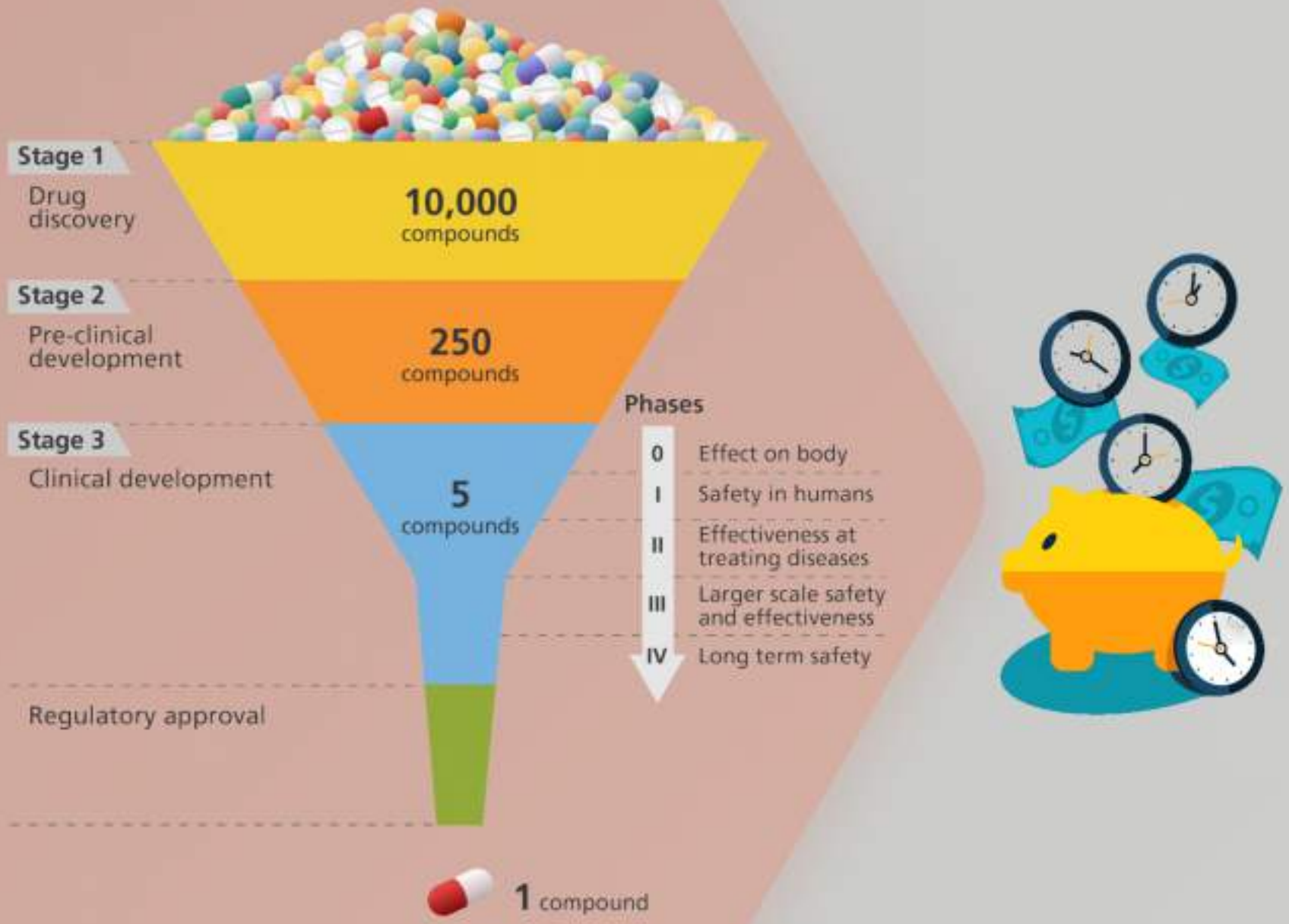
The Challenges

The Challenges

Cost


Stage 1
Drug discovery
10,000
compounds
Stage 2
Pre-clinical development
250
compounds
Stage 3
Clinical development
5
compounds
Regulatory approval
Phases
0 Effect on body
I Safety in humans
II Effectiveness at treating diseases
III Larger scale safety and effectiveness
IV Long term safety
1 compound

The Challenges

Cost

The Challenges

Cost

Unpredictability

In-vitro

≠

In-vivo

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Clinical response

The Challenges

Cost

Unpredictability

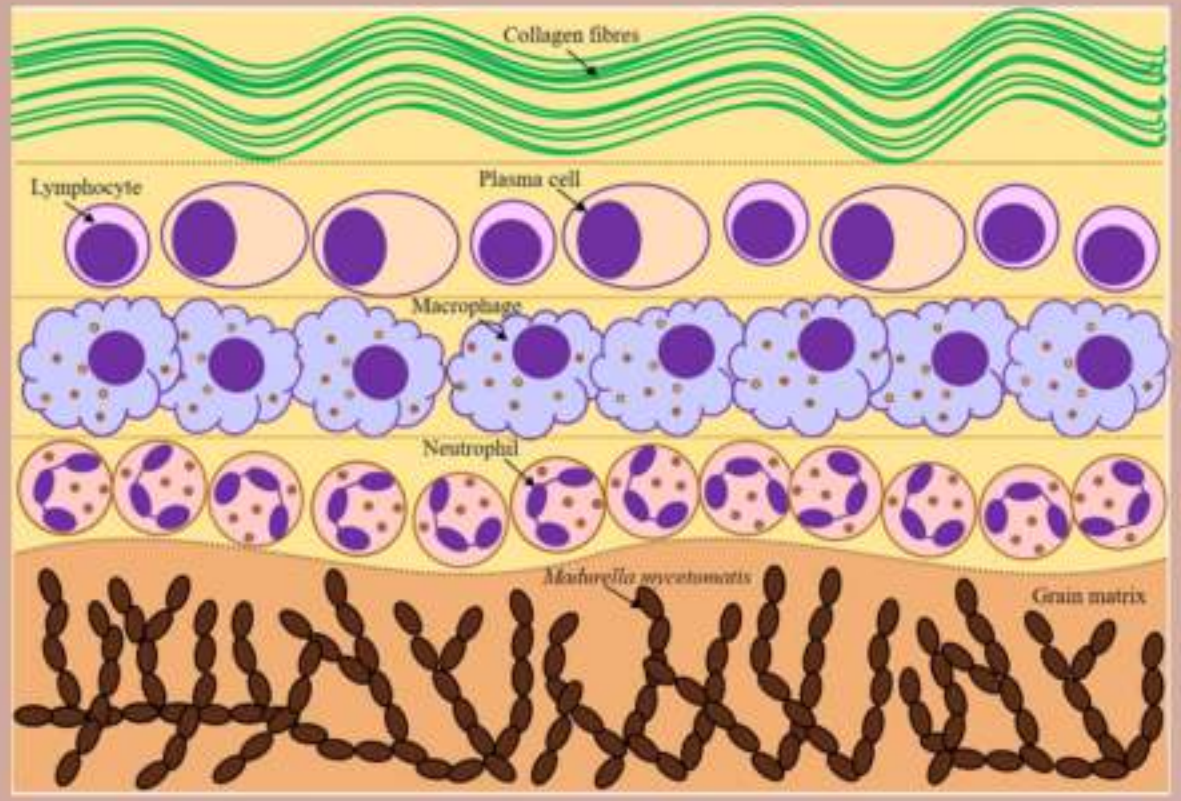
The Challenges

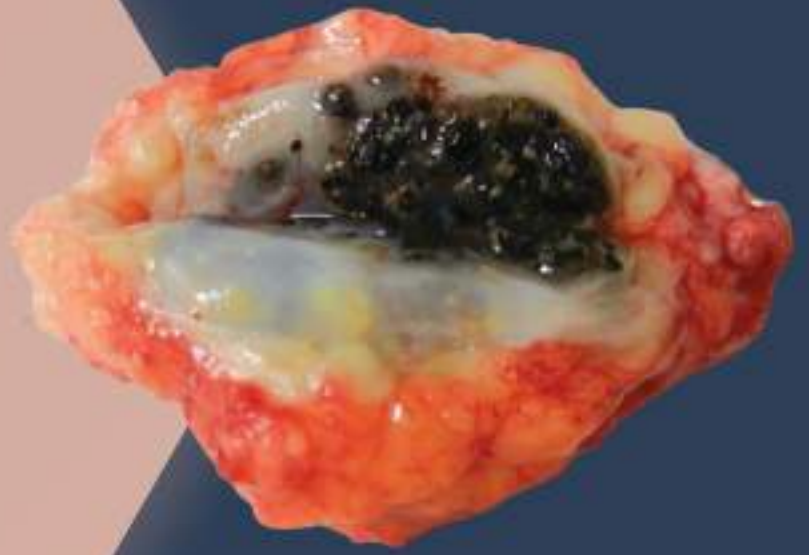
Cost

Unpredictability

The Grain

Protective barriers





The Challenges

Cost

Unpredictability

The Grain

The Challenges

Phenotypic Screening

Drug Repurposing

Phenotypic Screening

Drug Repurposing

Phenotypic Screening

Drug Repurposing

The Challenges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Design and synthesis Novel Chemical Entities that are Uniquely Active against *Madurella mycetomatis*

(the most common causative fungi of Eumycetoma)

Via Phenotypic Screening

Design and synthesis Novel Chemical Entities that are Uniquely Active against *Madurella mycetomatis*

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Via Phenotypic Screening


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Methodology

Phenotypic screening for hits

Preliminary screening

vs

chemical library
of
45 compounds

Madurella mycetoatis
reference strains
mm55

XTT viability assay

Preliminary screening

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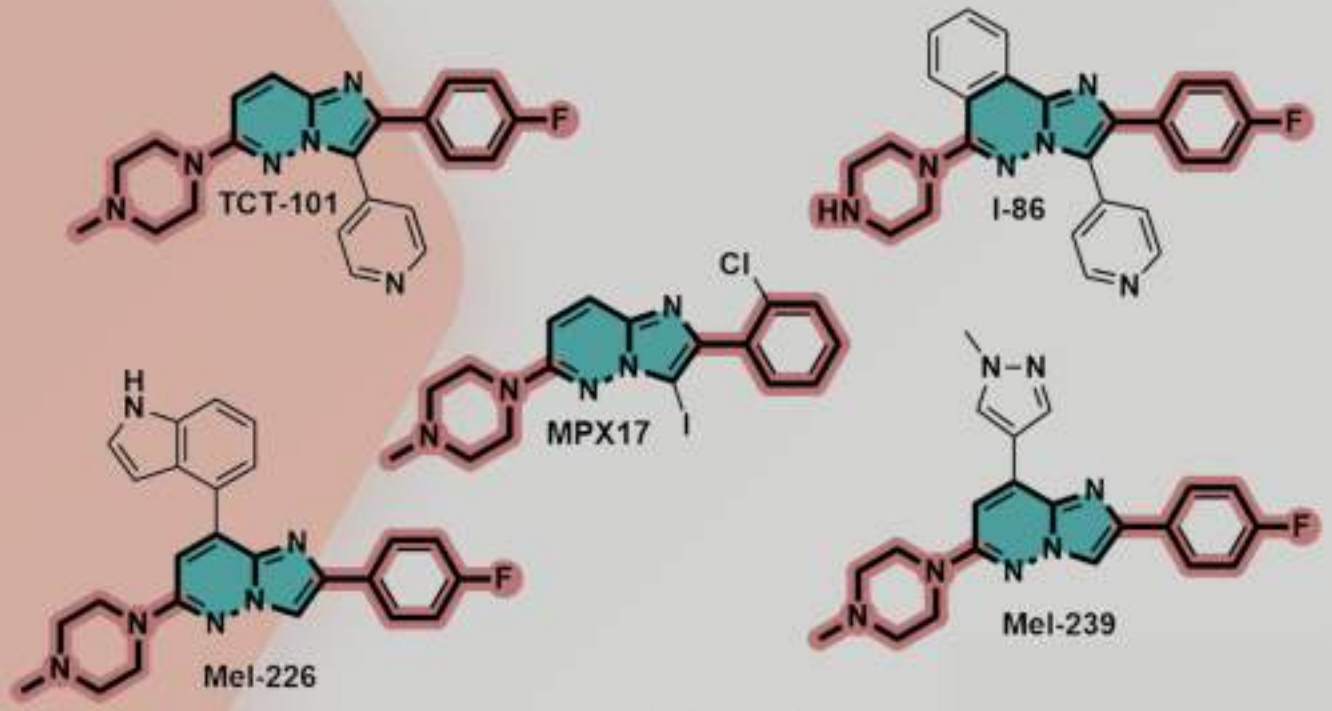


5 Hits

Methodology

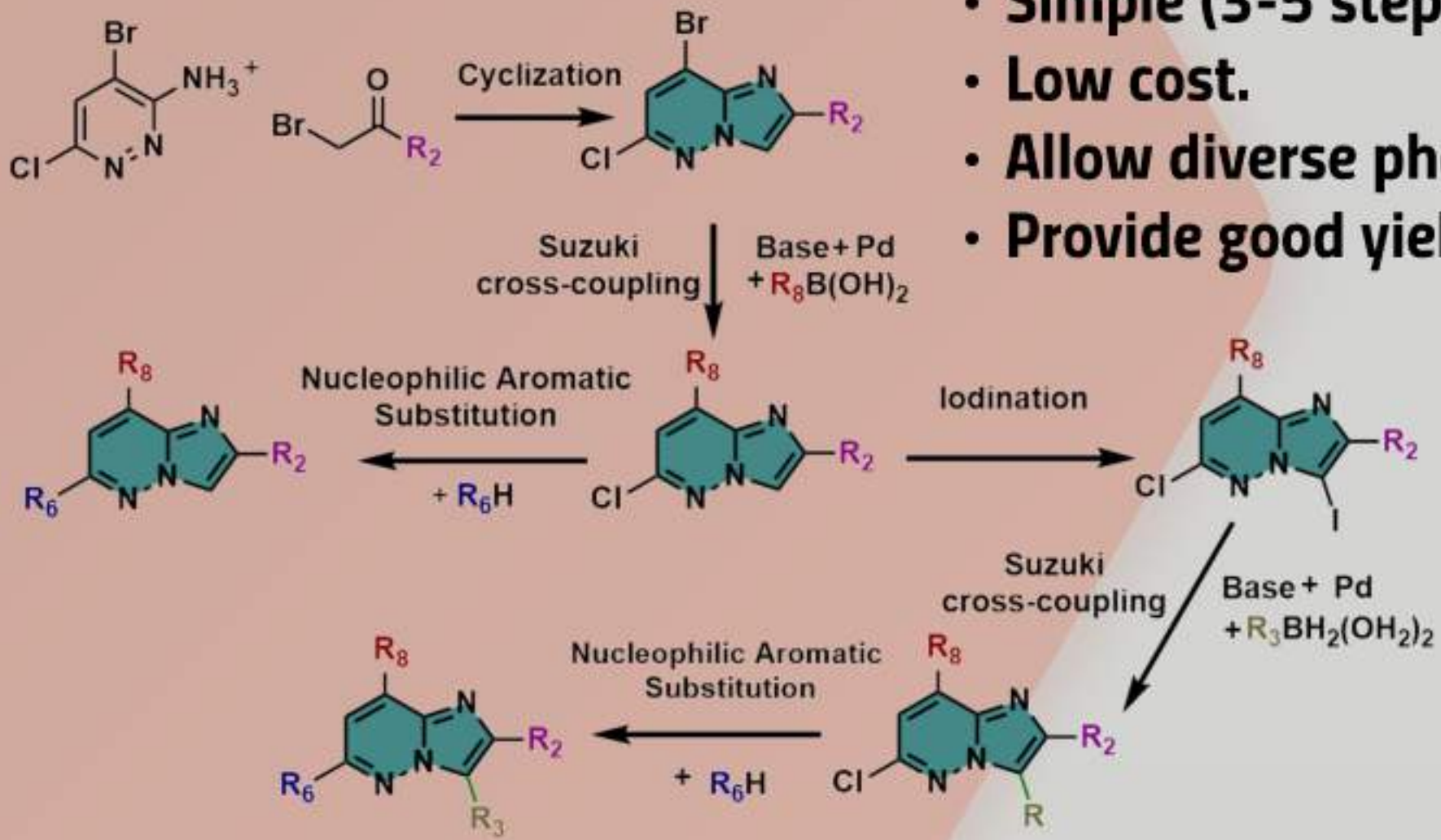
Phenotypic screening for hits

Methodology

Phenotypic screening for hits

Hits library expansion

Developing a synthetic route



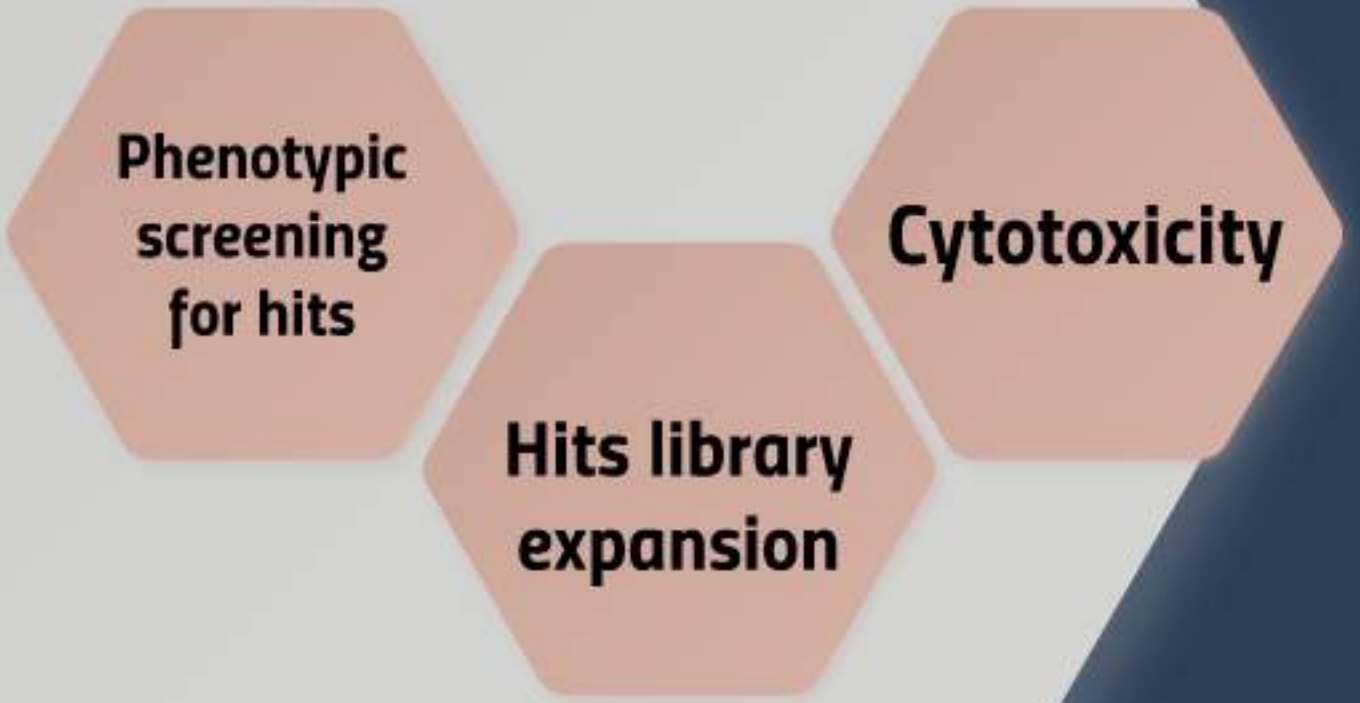
- **Simple (3-5 steps).**
- **Low cost.**
- **Allow diverse pharmacomodulations.**
- **Provide good yields.**

Methodology

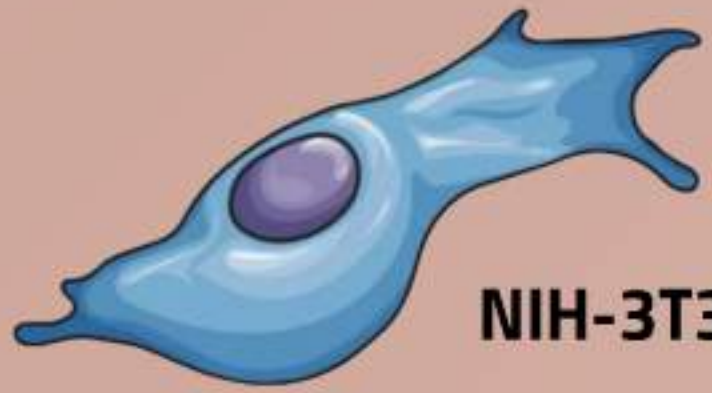
Phenotypic screening for hits

Hits library expansion

Methodology



Basal Cytotoxicity

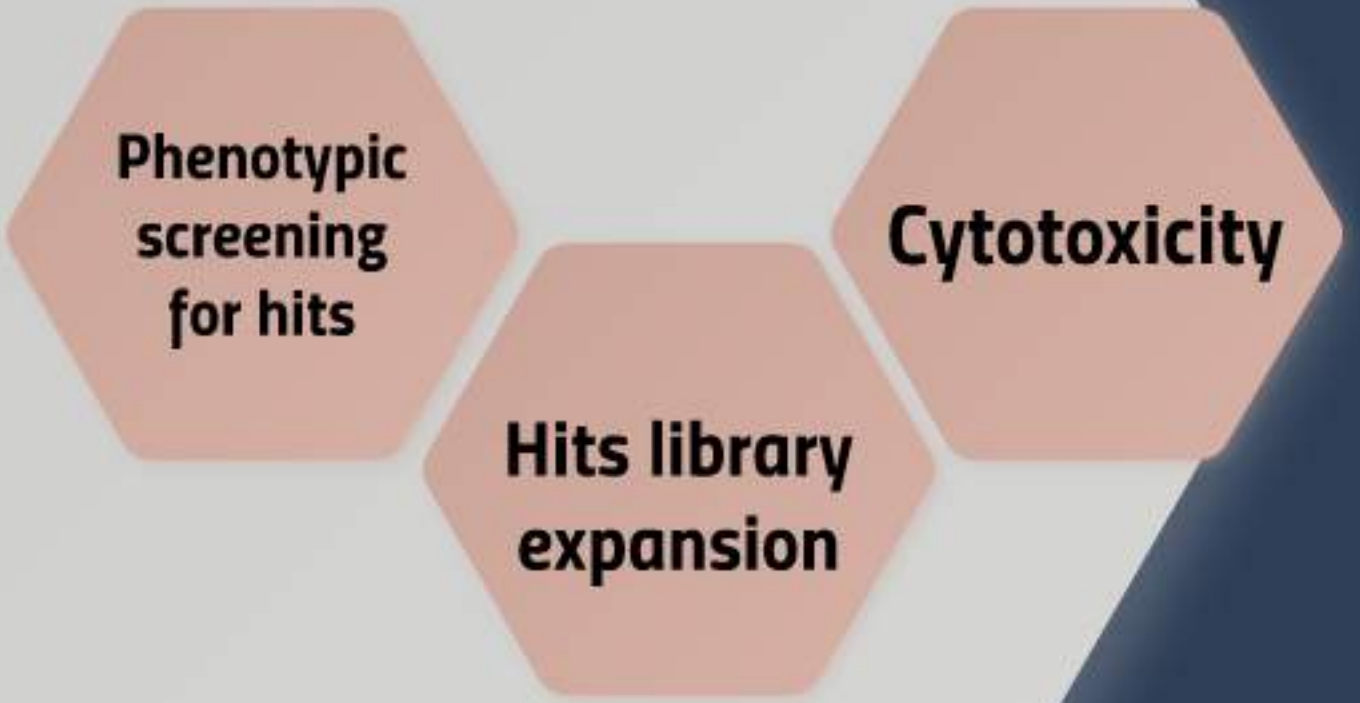


NIH-3T3 Fibroblasts

Our products
VS
Itraconazole and AmB

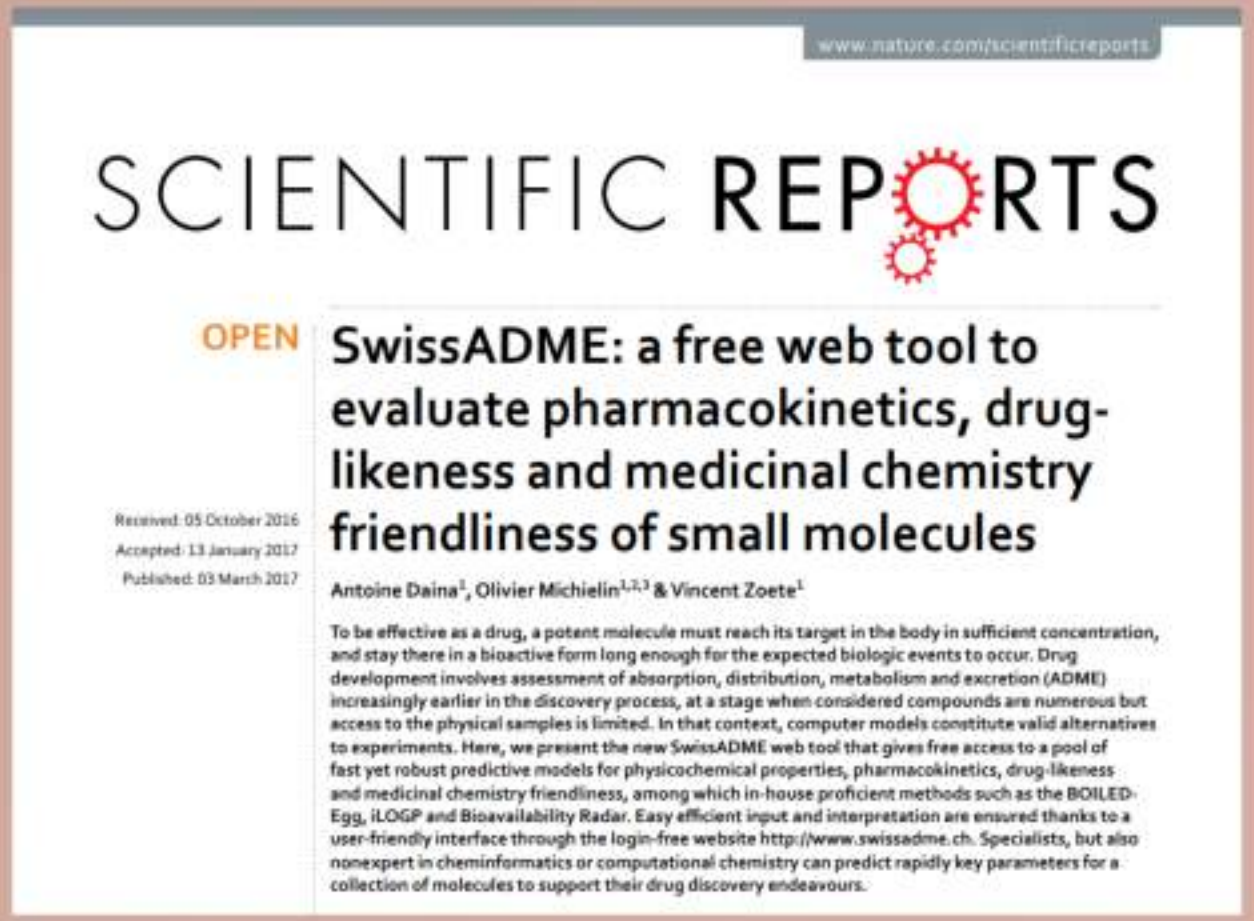
MTT viability Assay

Methodology



Methodology

SwissADME prediction Tool



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SCIENTIFIC REPORTS

OPEN

SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules

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Accepted: 13 January 2017
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Antoine Daina[1], Olivier Michielin[1,2,3] & Vincent Zoete[1]

To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the discovery process, at a stage when considered compounds are numerous but access to the physical samples is limited. In that context, computer models constitute valid alternatives to experiments. Here, we present the new SwissADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability Radar. Easy efficient input and interpretation are ensured thanks to a user-friendly interface through the login-free website http://www.swissadme.ch. Specialists, but also nonexpert in cheminformatics or computational chemistry can predict rapidly key parameters for a collection of molecules to support their drug discovery endeavours.

Absorption
Distribution
Metabolism
Excretion

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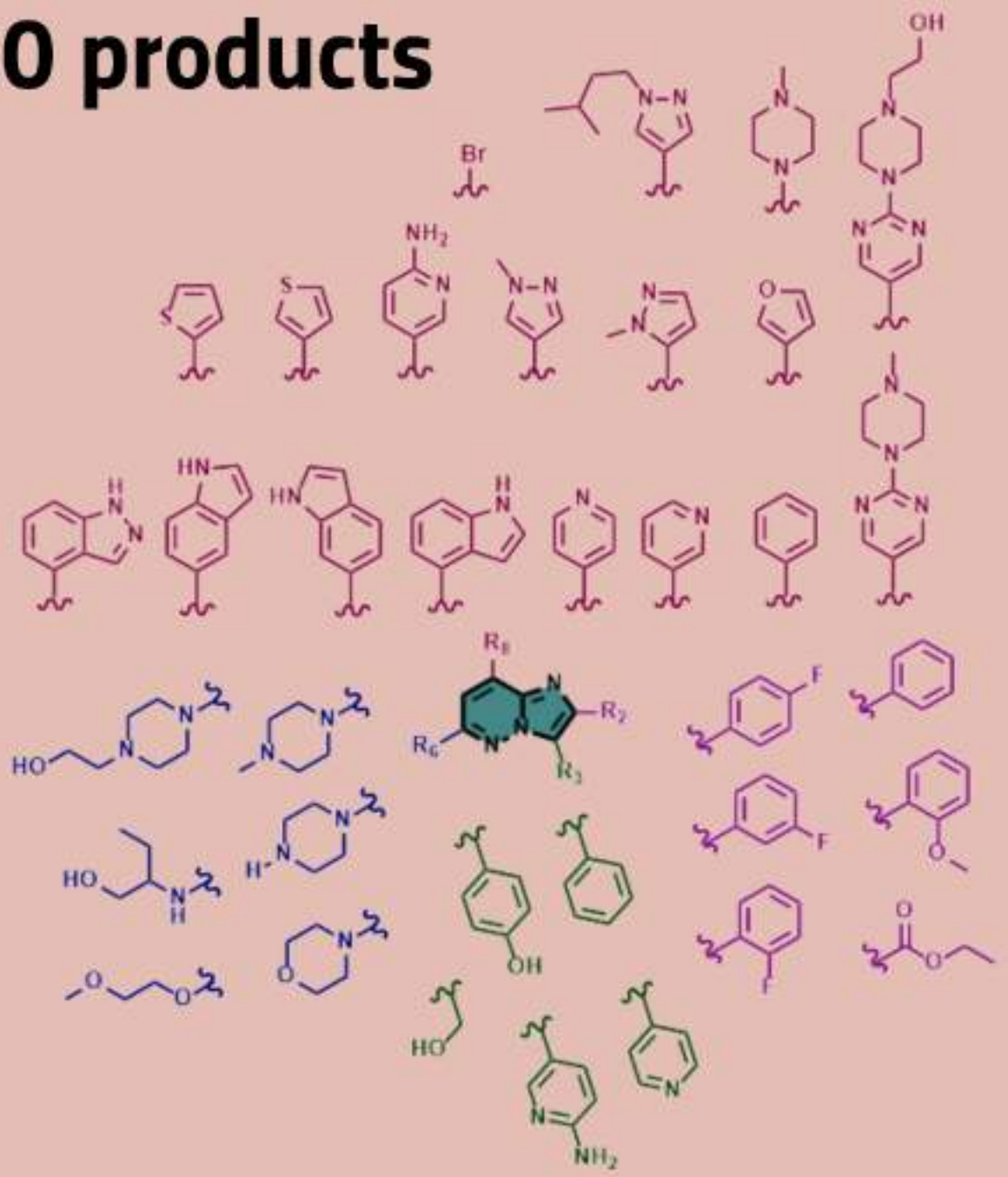
Results

Synthesized products

60 products



- 150 reactions.
- Diverse pharmacomodulations.
- Good purity.
- Good yields.

Results

Synthesized products

Results

Synthesized products

Activity and Cytotoxicity

IC50s (Efficacy vs Toxicity)

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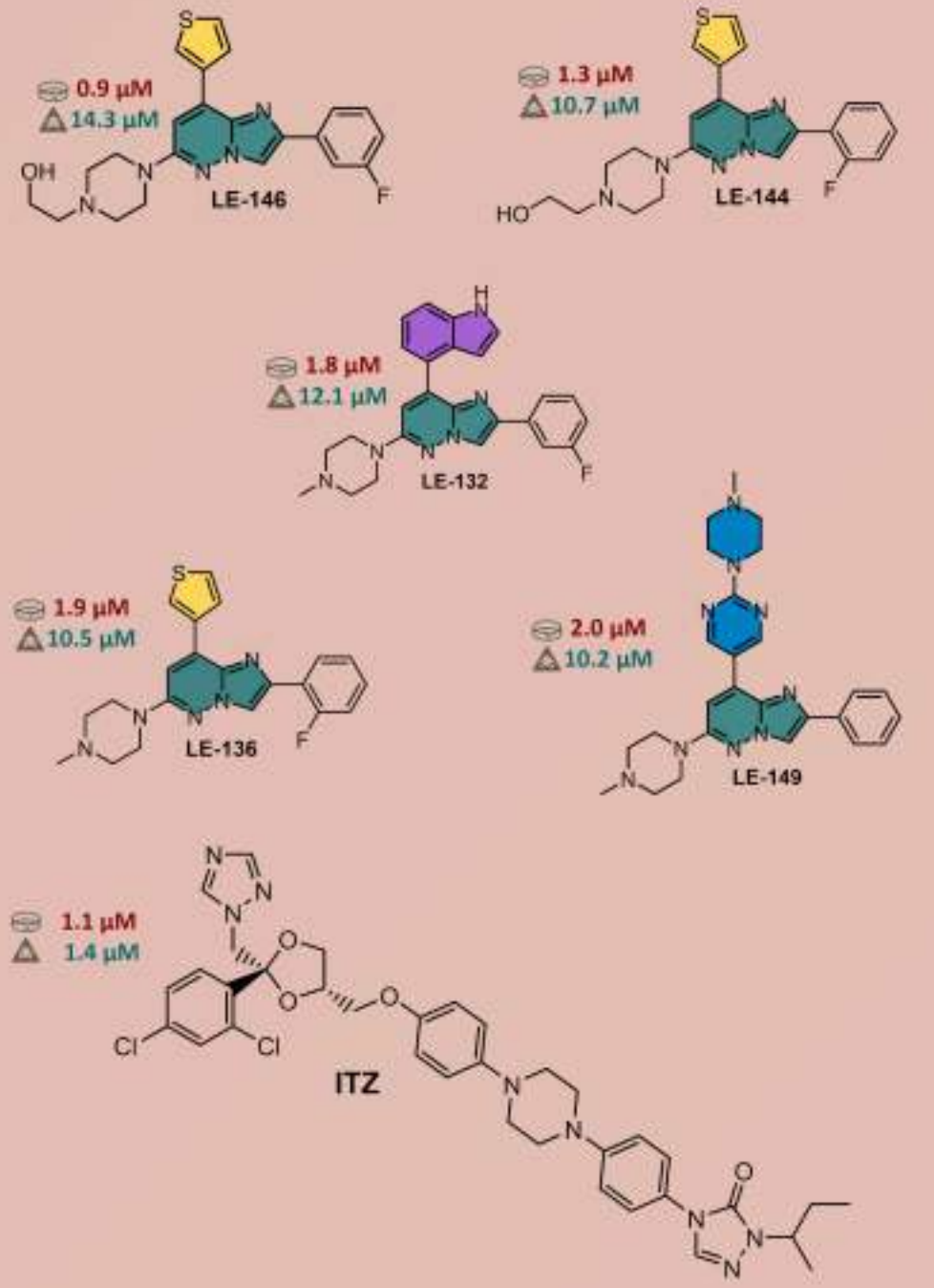
- **5** products had an **IC50 ≤ 2 µM** with 1 product **LE-146** with an **IC50 of 0.9 µM** (less than I**TZ, IC50 = 1.1 µM**)



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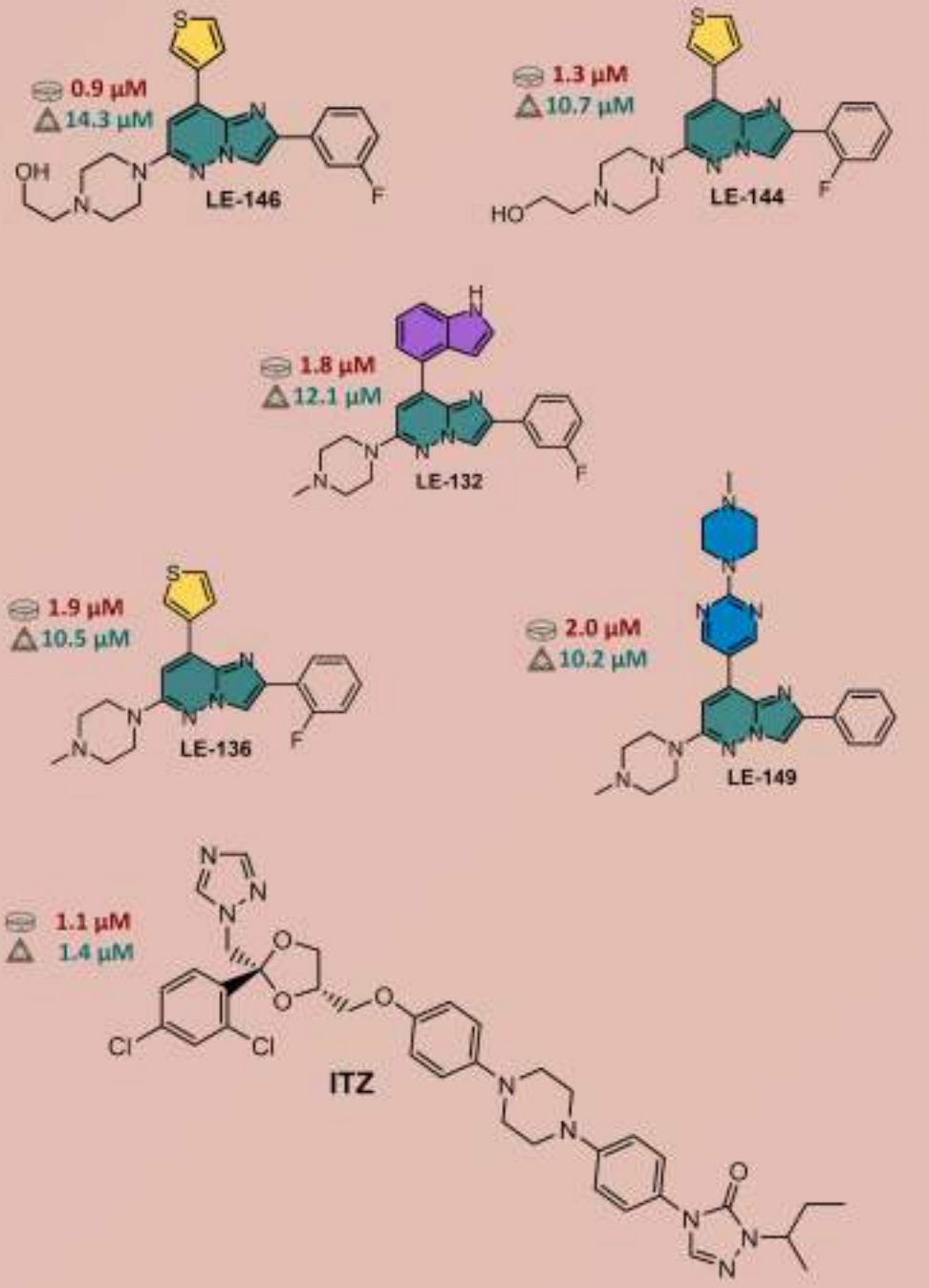

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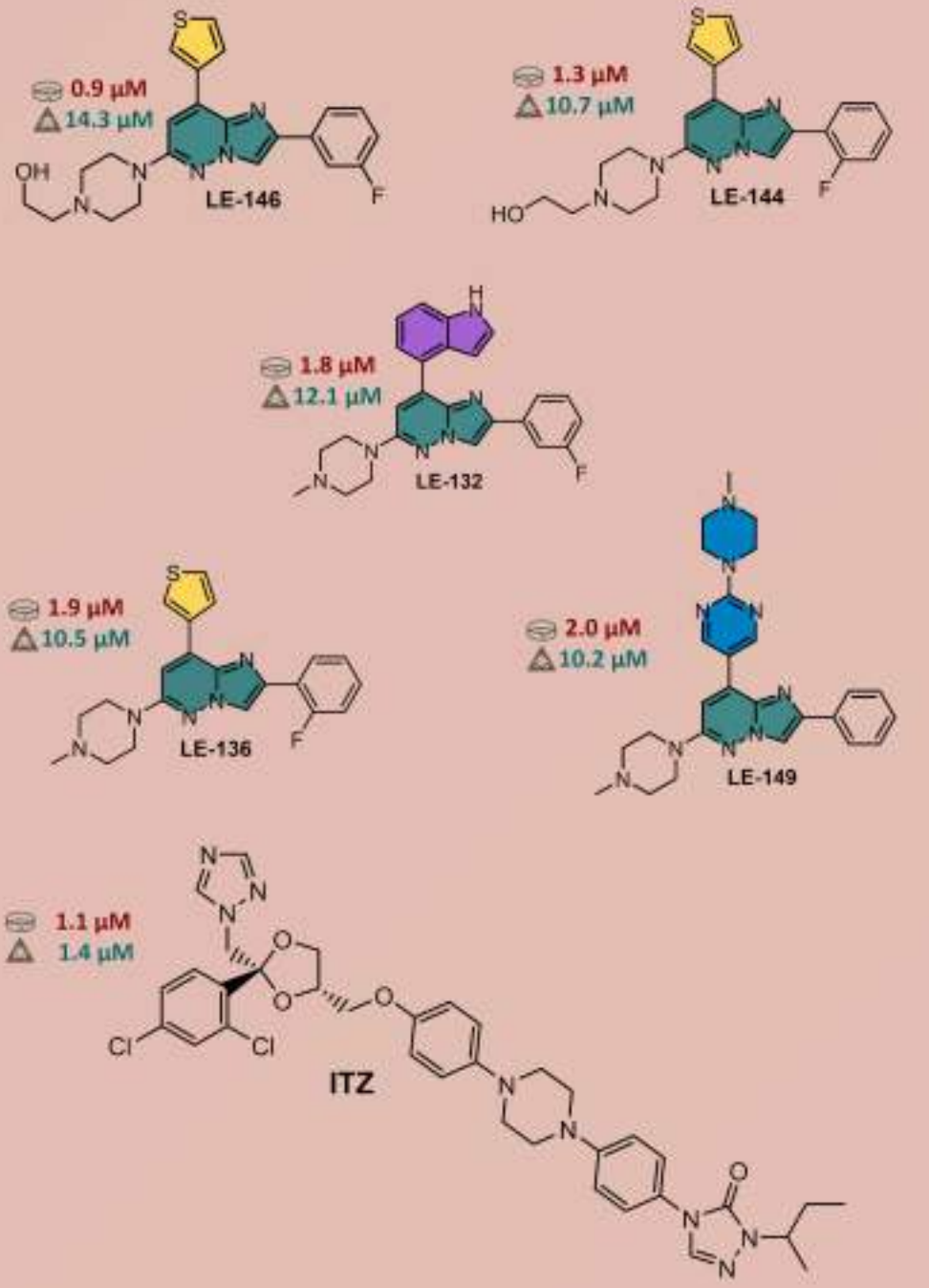
- Much **simpler structure** compared to ITZ



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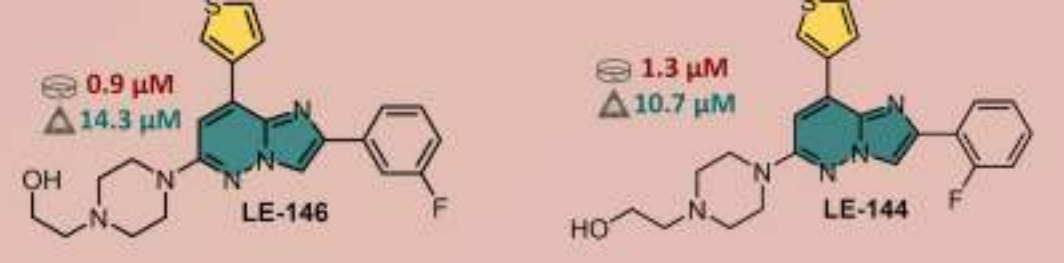
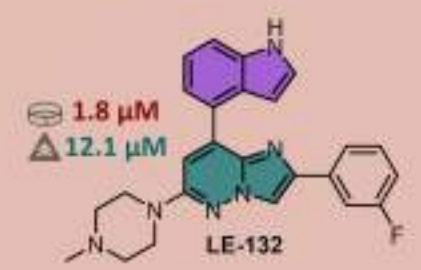
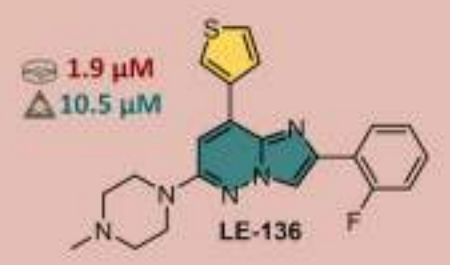
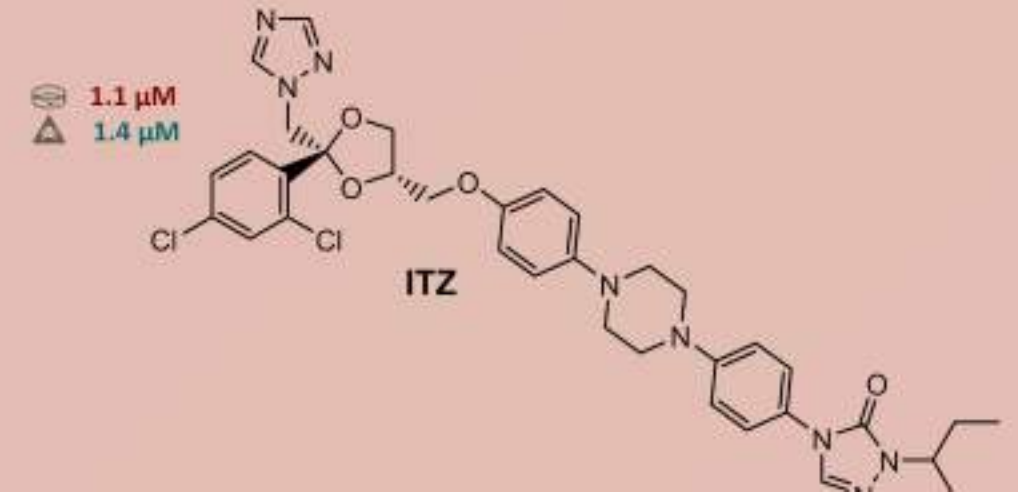






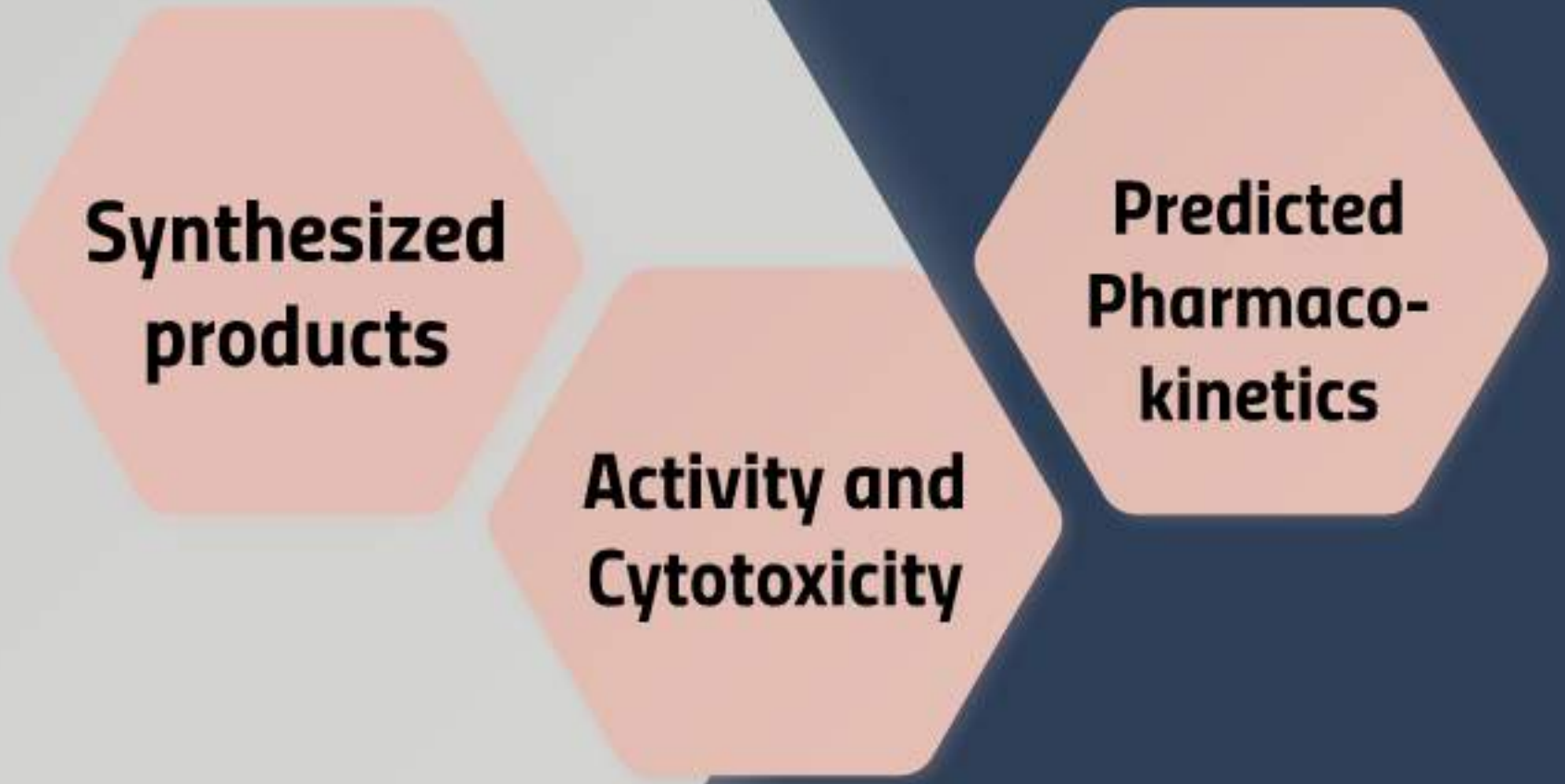


Results

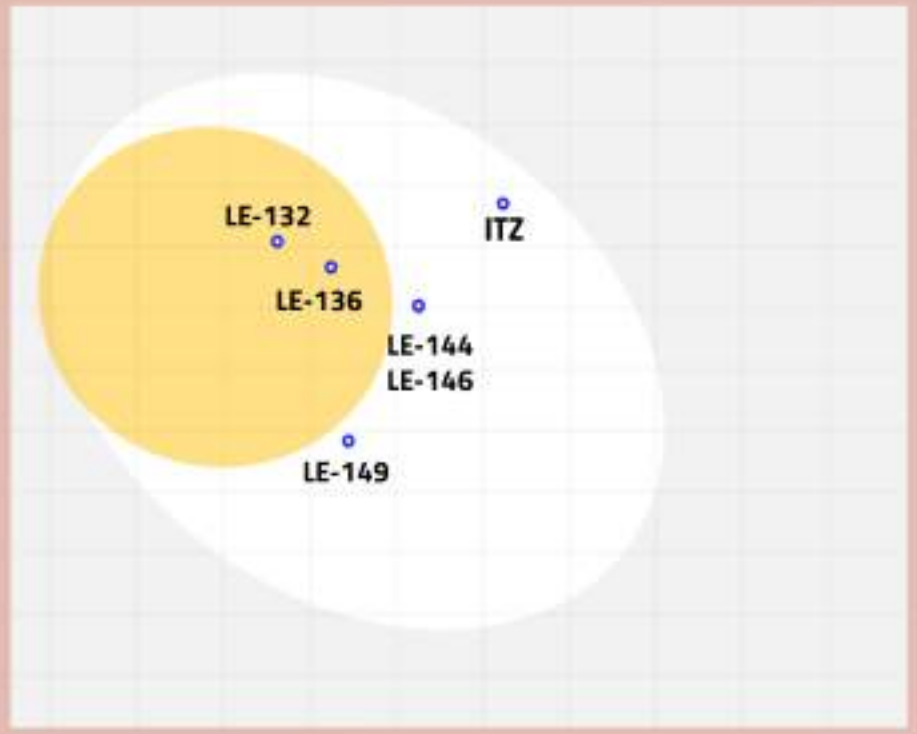
Synthesized products

Activity and Cytotoxicity

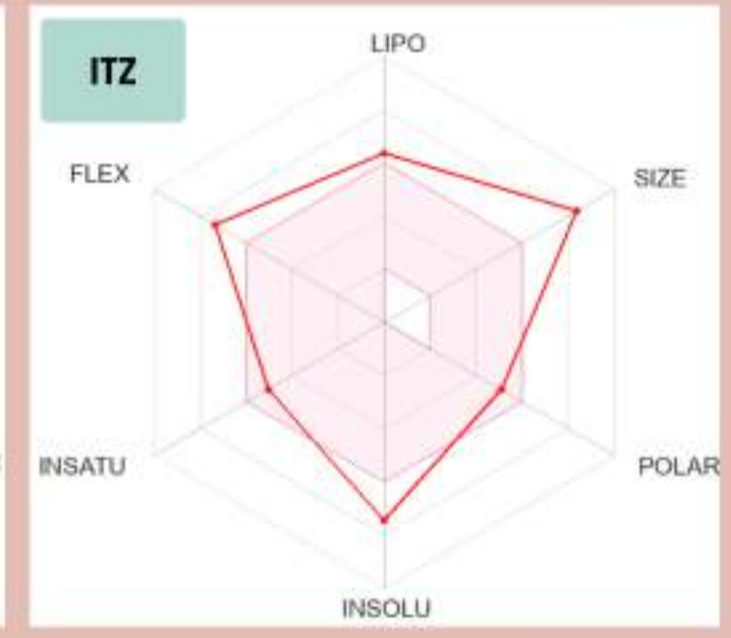
Results


Synthesized products
Activity and Cytotoxicity
Predicted Pharmaco-kinetics

The Boiled Egg



Bioavailability Radar



Optimal range for each physicochemical property

High probability of passive absorption by the GIT.

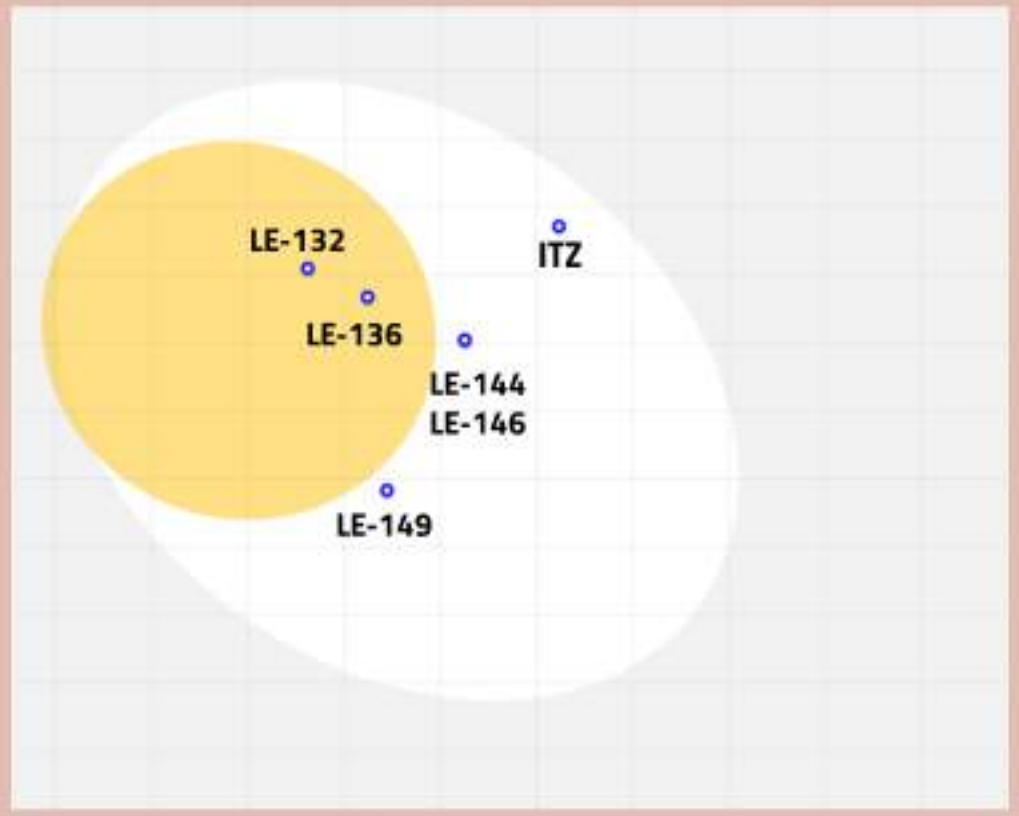
High probability of brain penetration.

Non-substrate of P-gp.

Actively effluxed by P-gp.

Lipophilicity	Size	Polarity
Saturation	Flexibility	Solubility (log S)

The Boiled Egg



Bioavailab

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Siz

Saturation

Flexi

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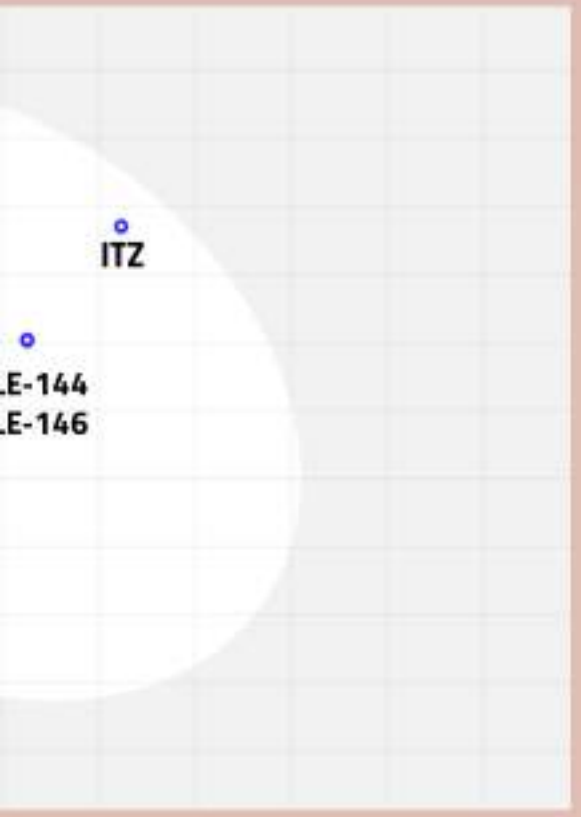

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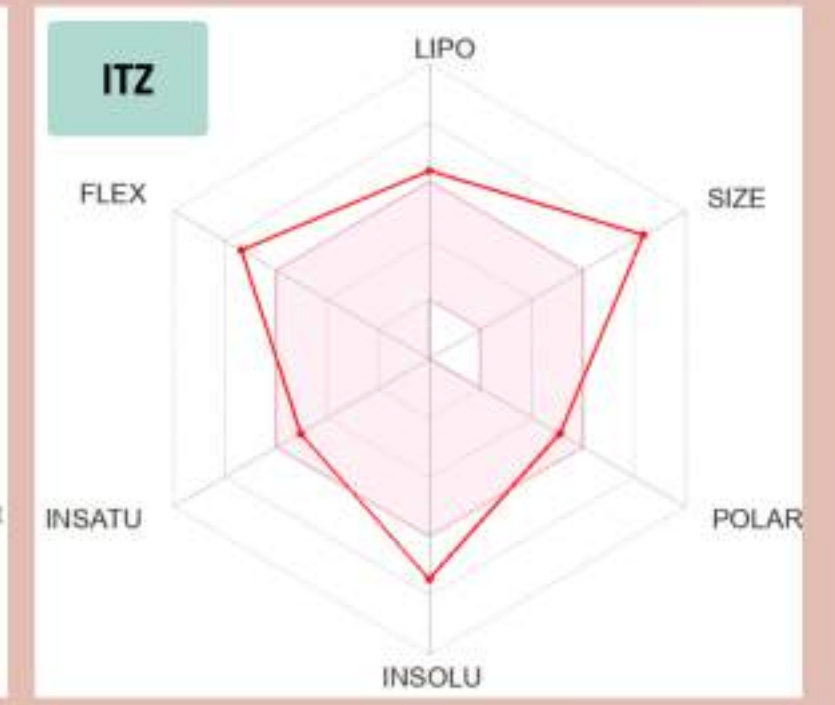

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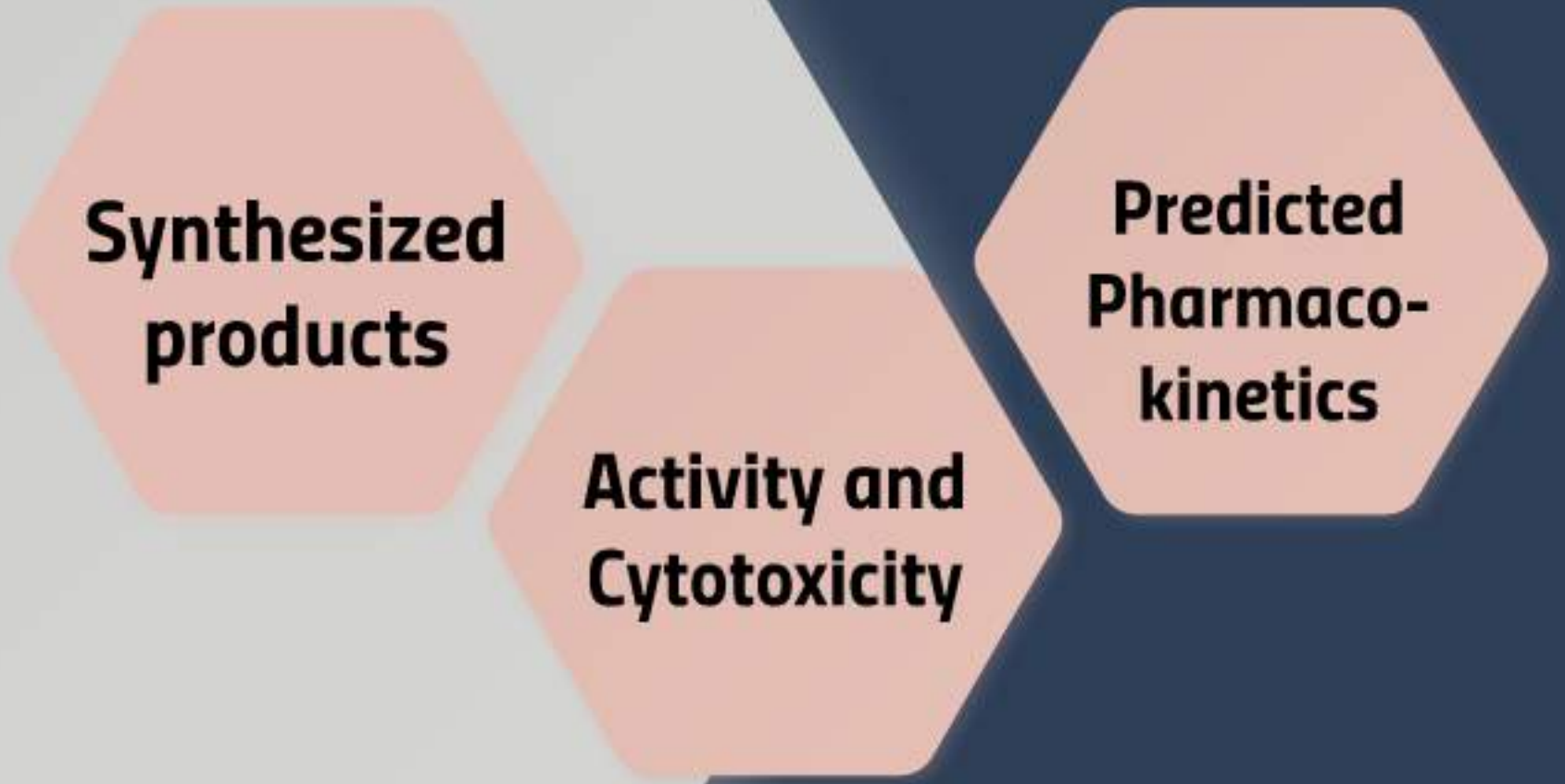
Results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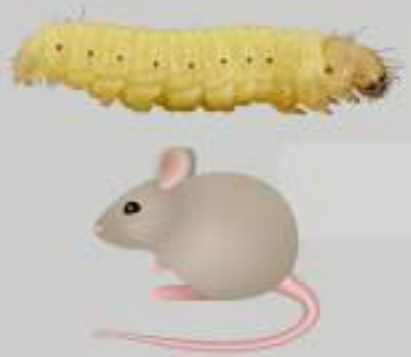
More studies are needed

***In-vivo* evaluation using *Galleria mellonella* larvae and mice**

More studies are needed



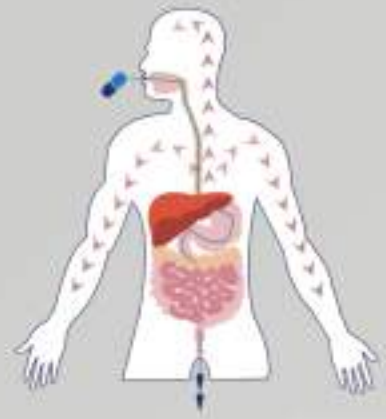
In-vivo evaluation using *Galleria mellonella* larvae and mice

Proteomics and Transcriptomics to determine the molecular target

More studies are needed

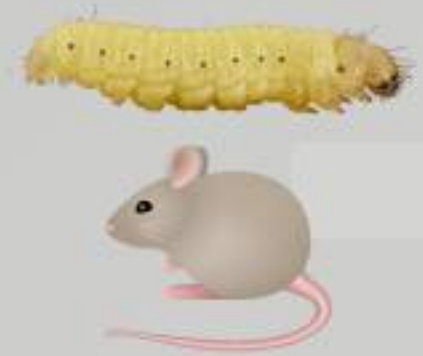
In-vivo evaluation using *Galleria mellonella* larvae and mice

Proteomics and Transcriptomics to determine the molecular target



Pharmacokinetics and Pharmacodynamics studies

More studies are needed



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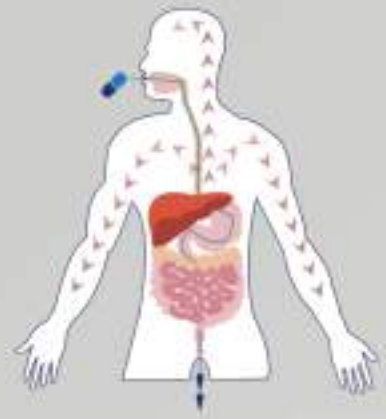
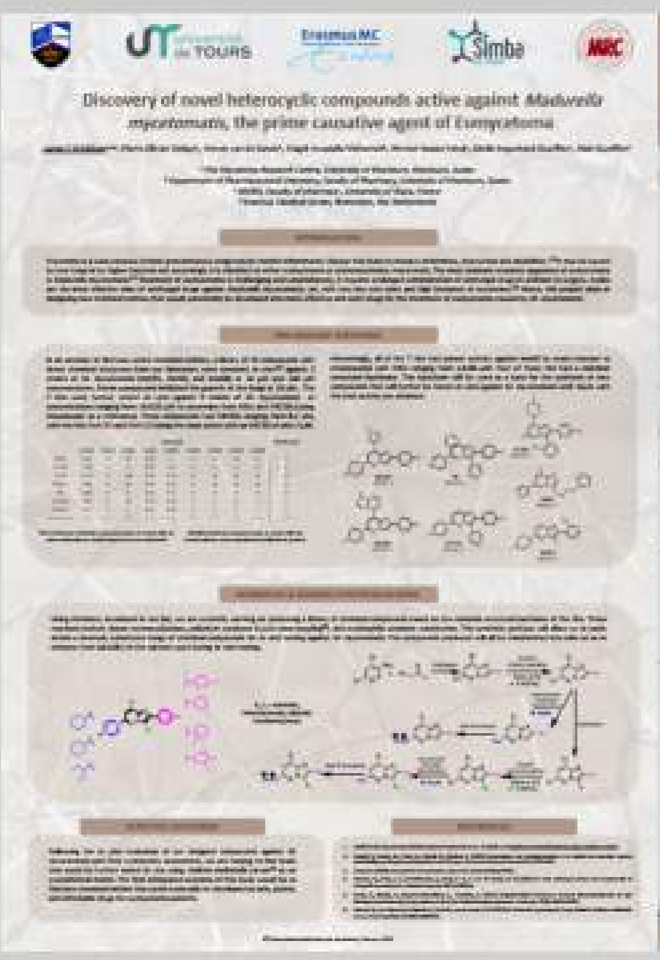


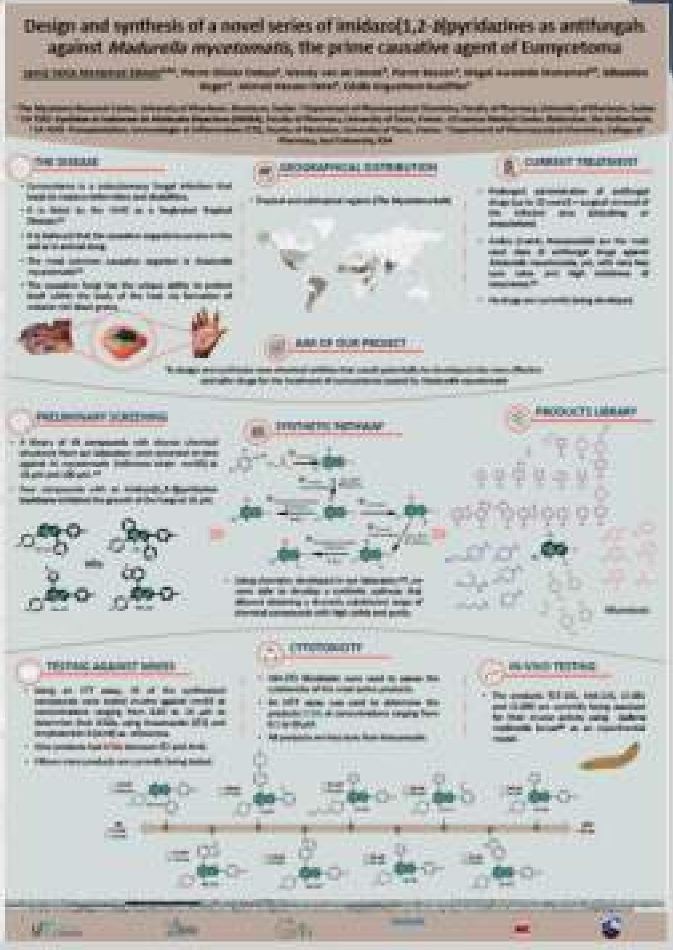
Pharmacokinetics and Pharmacodynamics studies

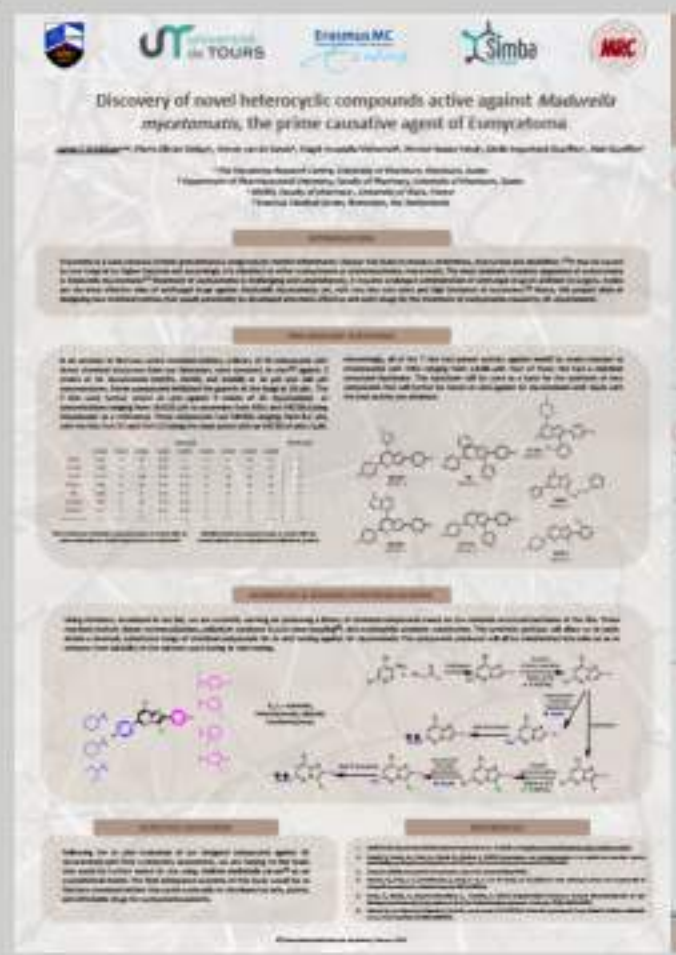
Computational studies to design more potent compounds

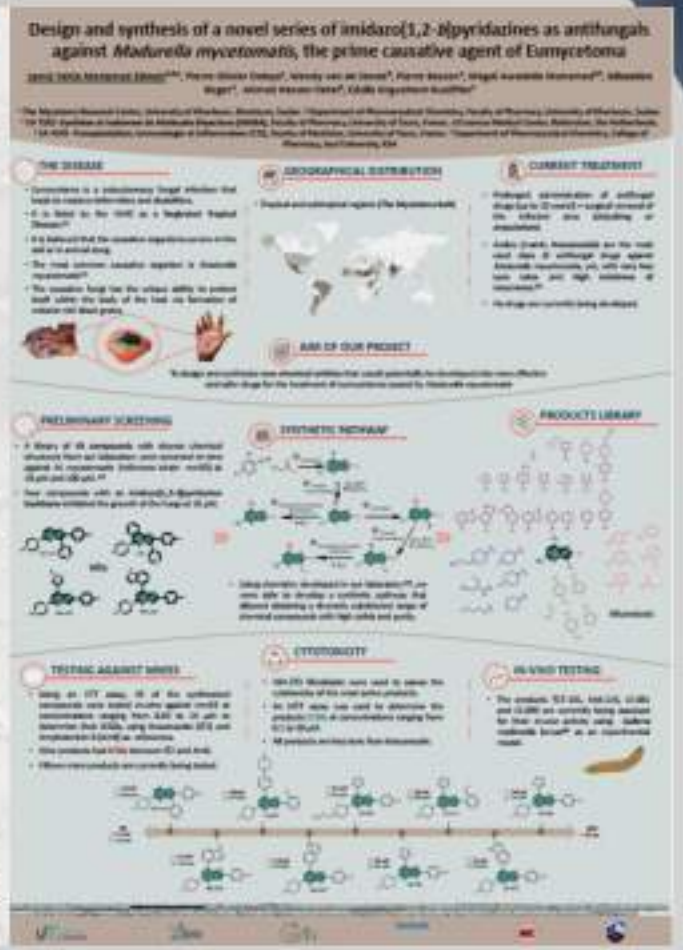
More studies are needed


Scientific contributions
The Challenges
Prospects
Drug discovery for Eumycetoma
Objective
Results
Methodology


Discovery of novel heterocyclic compounds active against Madurella mycetomatis, the prime causative agent of Eumycetoma


Design and synthesis of a novel series of imidazo[1,2-b]pyridazines as antifungals against Madurella mycetomatis, the prime causative agent of Eumycetoma
THE DISEASE
GEOGRAPHICAL DISTRIBUTION
CURRENT TREATMENT
AIM OF OUR PROJECT
PRELIMINARY SCREENING
SYNTHETIC PATHWAY
PRODUCTS LIBRARY
CYTOTOXICITY
IN-VIVO TESTING





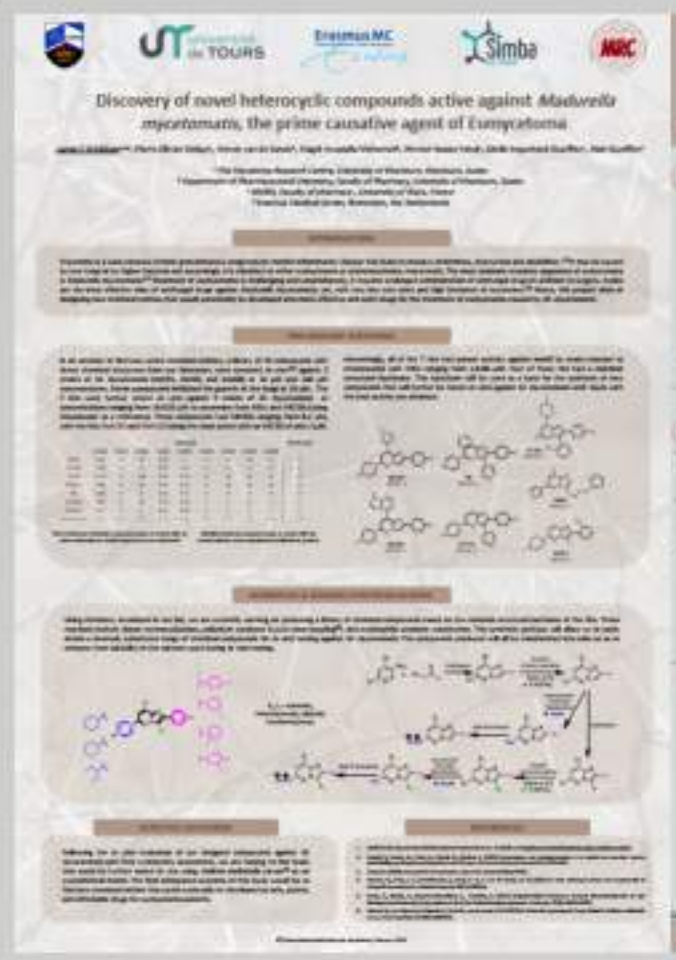
PLOS NEGLECTED TROPICAL DISEASES

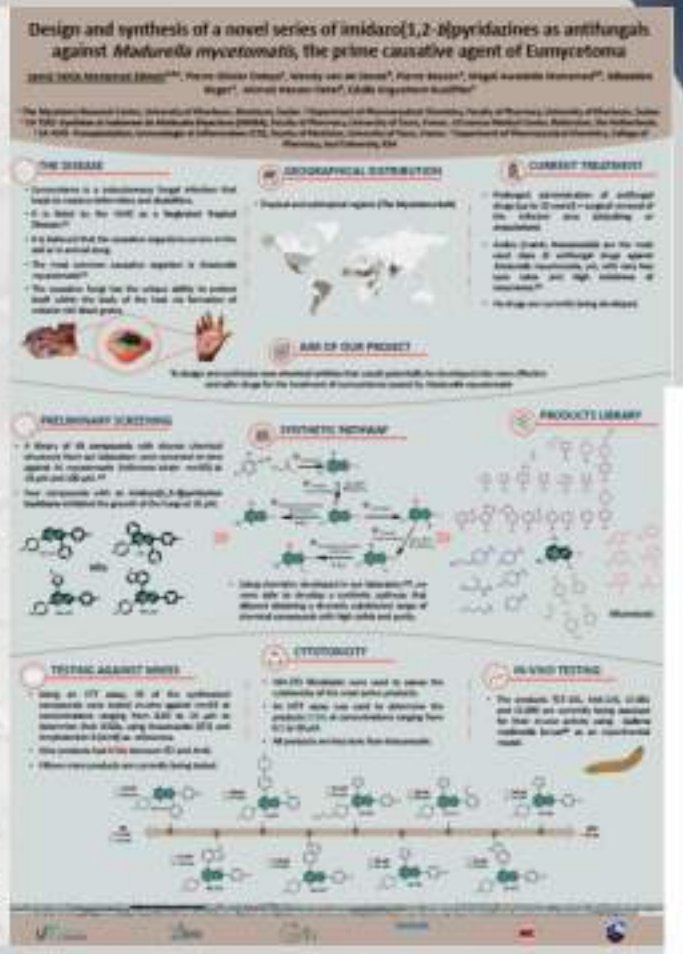
OPEN ACCESS

REVIEW

Madurella mycetomatis causing eumycetoma medical treatment: The challenges and prospects

Lamis Y. M. Elkheir, Rayan Haroun, Magdi Awadalla Mohamed, Ahmed Hassan Fahal





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European Journal of Medicinal Chemistry

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In Press, Journal Pre-proof ⓘ What's this?

Emerging Therapeutics: The imidazo[1,2-*b*]pyridazine scaffold as a novel drug candidate for eumycetoma, a neglected tropical disease ☆

Lamis Yahia Mohamed Elkheir [a b c], Pierre-Olivier Delaye [c], Mélanie Penichon [c], Kimberly Eadie [d], Magdi Awadalla Mohamed [e], Pierre Besson [f], Adélaïde Chesnay [g], Guillaume Desoubeaux [g], Sébastien Roger [f], Wendy Wilhelmina Johanna van de Sande [d], Ahmed Hassan Fahal [a], Cécile Enguehard-Gueiffier [c]


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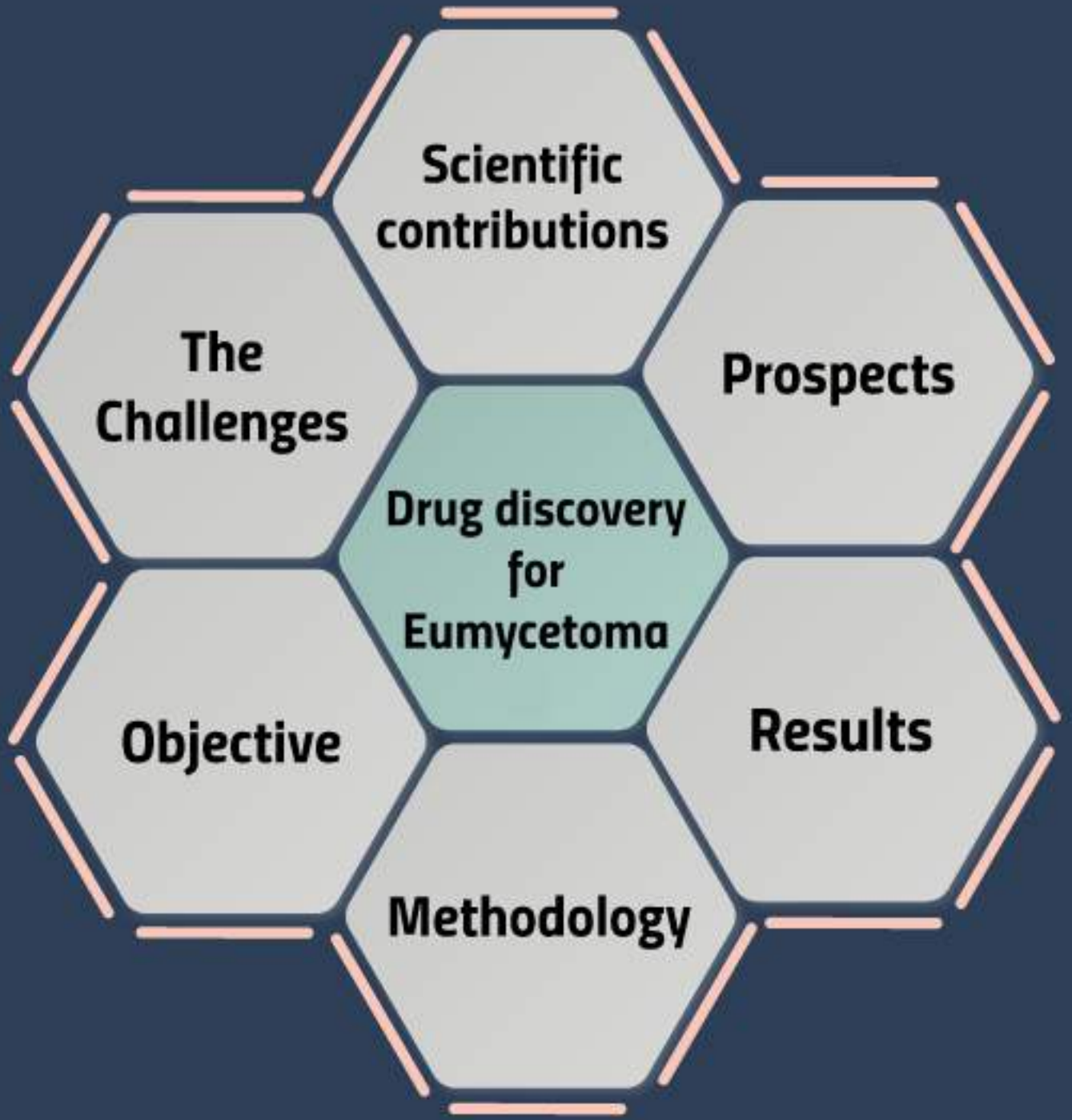
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Thank you for your kind attention !