

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



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



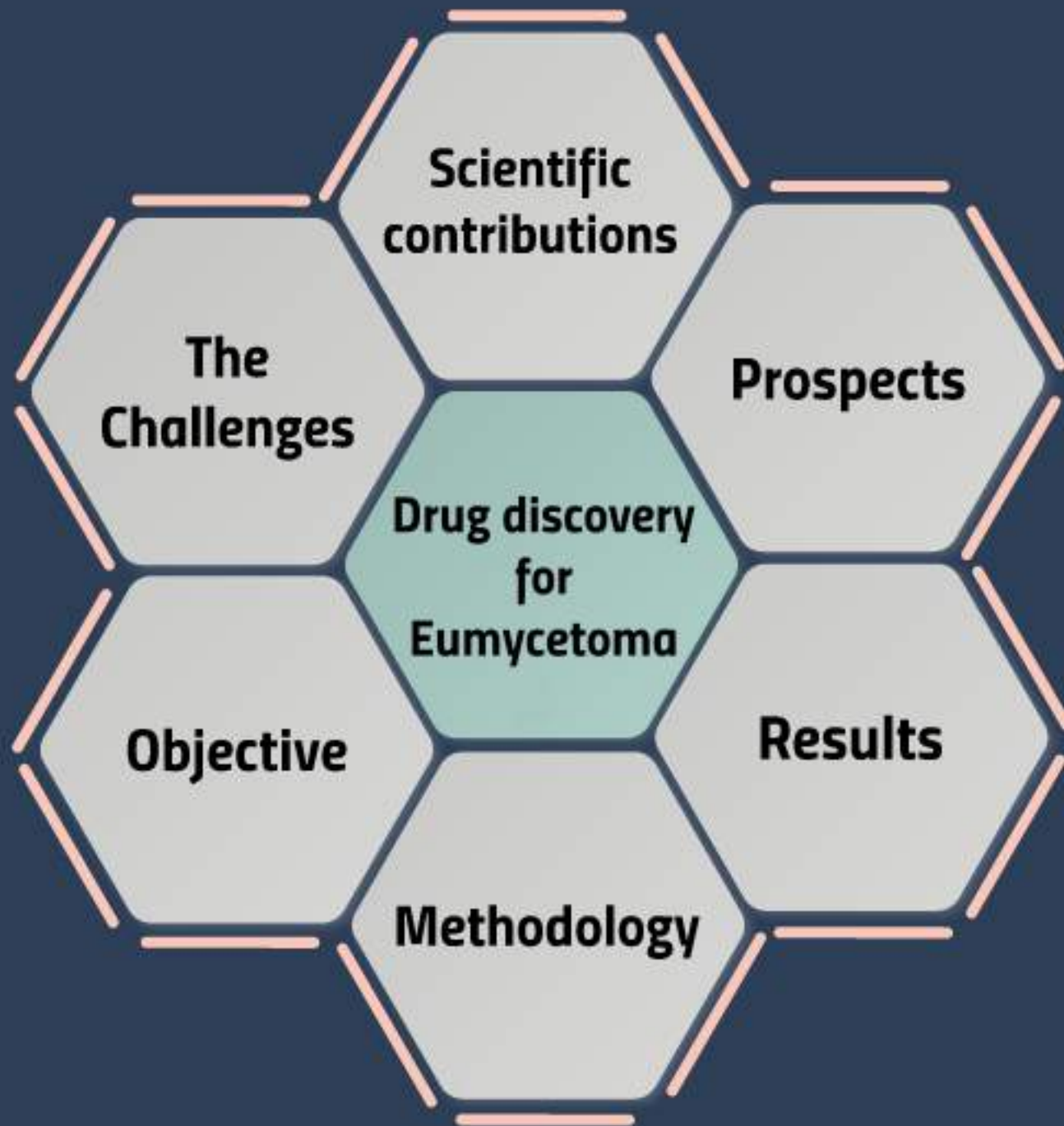
Dr. Pierre Bisson
Associate professor of Physiology
university of tours, France

Erasmus MC



Dr. Wendy van de Sande

Associate professor of Microbiology & Infectious Diseases,
Erasmus MC, the Netherlands



Eumycetoma

Mycetoma

What is Mycetoma?

What is Mycetoma?

- Mycetoma is a **chronic, destructive**, and **debilitating** infection of the subcutaneous tissue.



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- It most commonly affects the feet (Madura foot).



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What is Mycetoma?

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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 herdsman in rural areas.





Geographical Distribution (Mycetoma Belt)



Geographical Distribution (Mycetoma Belt)



Tropical and subtropical environment

Disease Progression



Microorganism
in thorns???

Disease Progression



Microorganism
in thorns???



Small nodule

Disease Progression



Microorganism
in thorns???



Small nodule

Disease Progression



Microorganism
in thorns???

Time??



Small nodule



Oozing sores

Disease Progression



Microorganism
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Small nodule



Oozing sores

Grains

Disease Progression



Microorganism
in thorns???



Small nodule



Oozing sores

Grains



Spread of infection to involve skin,
muscles, and bone

Disease Progression



Microorganism
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Small nodule



Oozing sores

Grains



Disfigurement



Spread of infection to involve skin,
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Disease Progression



Microorganism
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Small nodule



Oozing sores

Grains



Disfigurement
Disabilities



Spread of infection to involve skin,
muscles, and bone

Disease Progression



Microorganism
in thorns???



Small nodule



Oozing sores



Spread of infection to involve skin,
muscles, and bone

Disfigurement

Disabilities

Social stigma

Disease Progression



Microorganism
in thorns???



Small nodule



Oozing sores

Grains



Spread of infection to involve skin,
muscles, and bone

Disfigurement

Disabilities

Social stigma

Death

areas.

of



Tropical and subtropical environment



Treatment of Mycetoma



Treatment of Mycetoma

Actinomycetoma

Eumycetoma

Treatment of Mycetoma

Actinomycetoma

Antibiotics.

Few months of treatment.

90% cure rate.

Low recurrence rate

Eumycetoma

Treatment of Mycetoma

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Eumycetoma

Antifungals (azoles) + Surgery (excision or amputation)

Years of treatment.

25-35% cure rate.

High recurrence rate.

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Immense need for finding **NOVEL** drugs

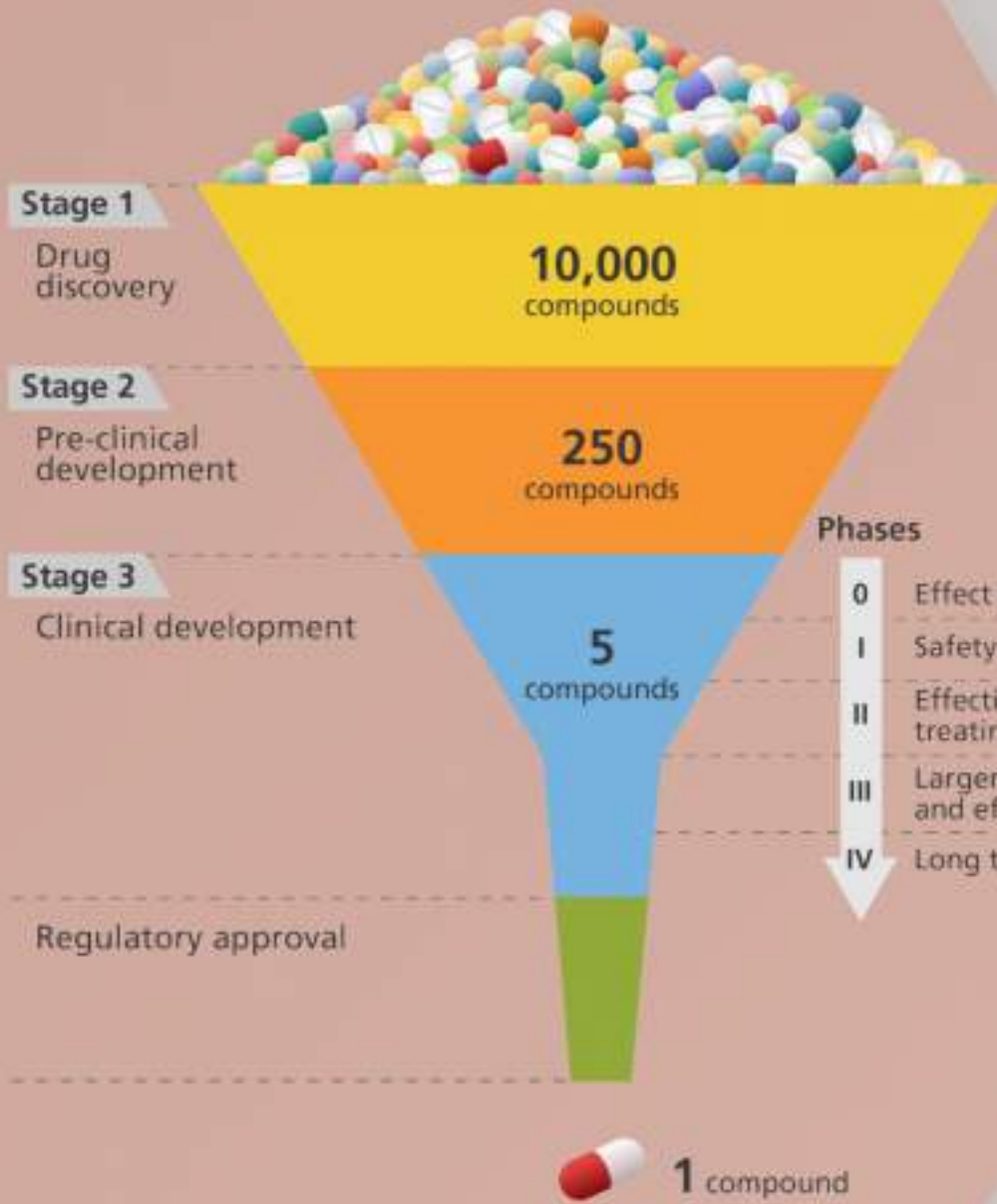




The Challenges

The Challenges





Phases

- 0 Effect on body
- I Safety in humans
- II Effectiveness at treating diseases
- III Larger scale safety and effectiveness
- IV Long term safety



The Challenges



The Challenges



Cost

Unpredictability

In-vitro



In-vivo



Clinical response



The Challenges



Cost

Unpredictability

The Challenges

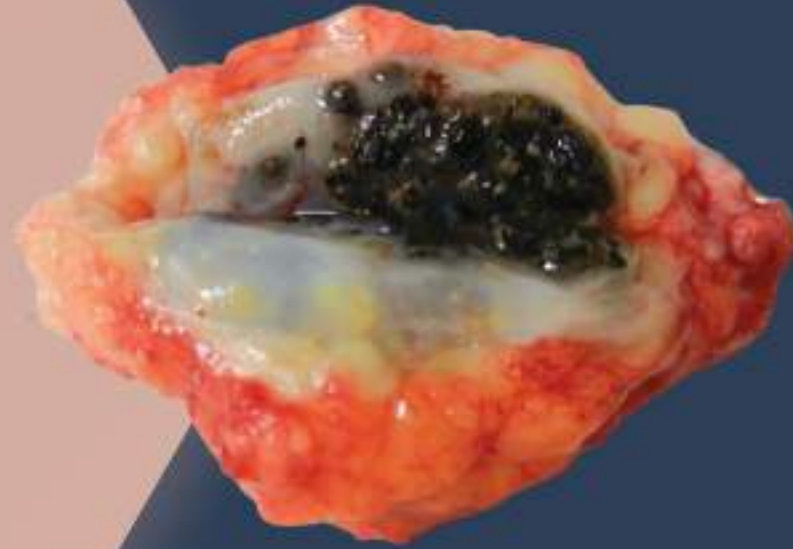
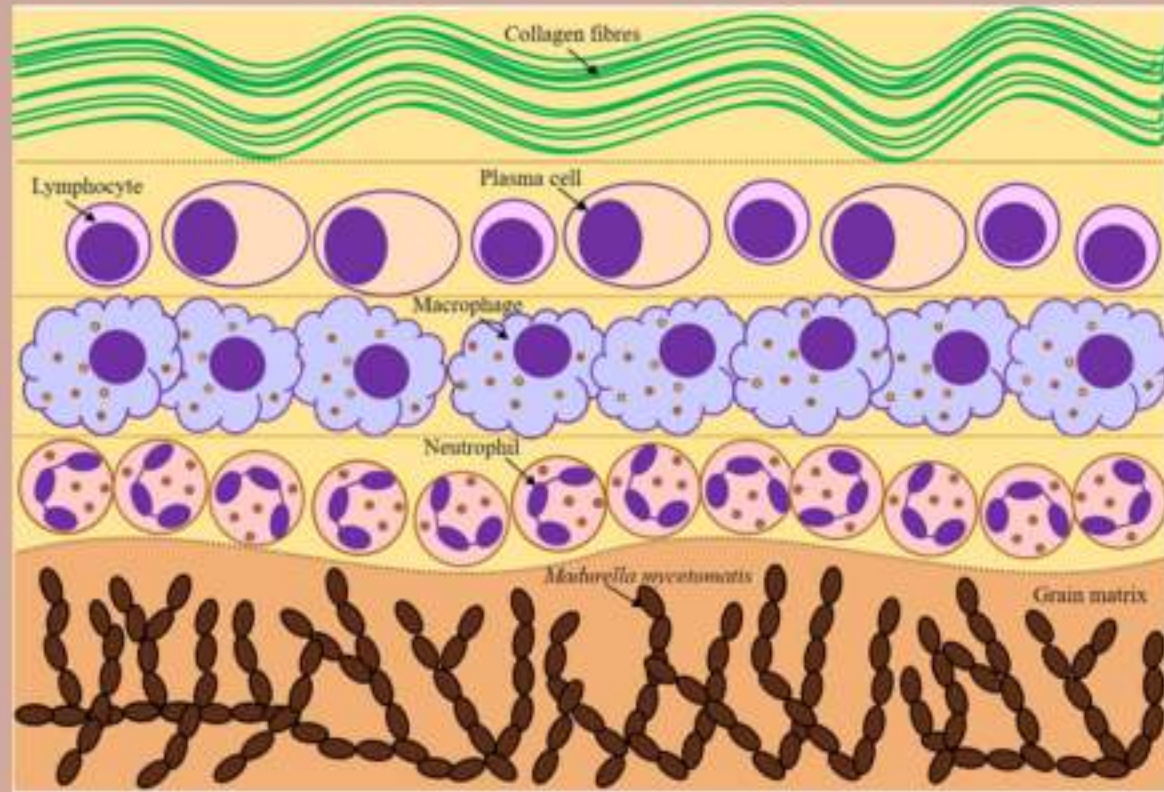


Cost

Unpredictability

The Grain

Protective barriers



The Challenges



Cost

Unpredictability

The Grain

The Challenges



Cost

Unpredictability

The Grain

**Unexplored
biology**

Phenotypic Screening

Drug Repurposing

Phenotypic Screening



Drug Repurposing

Phenotypic Screening



Drug Repurposing



The Challenges

Cost

Unpredictability

The Grain

**Unexplored
biology**



**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
(the most common causative fungi of Eumycetoma)**

**Via Phenotypic
Screening**





Methodology

Methodology

**Phenotypic
screening
for hits**

Preliminary screening



VS



chemical library
of
45 compounds

Madurella mycetozitica
reference strains
mm55

XTT viability assay

Preliminary screening



VS



chemical library
of
45 compounds

Madurella mycetozitica
reference strains
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XTT viability assay

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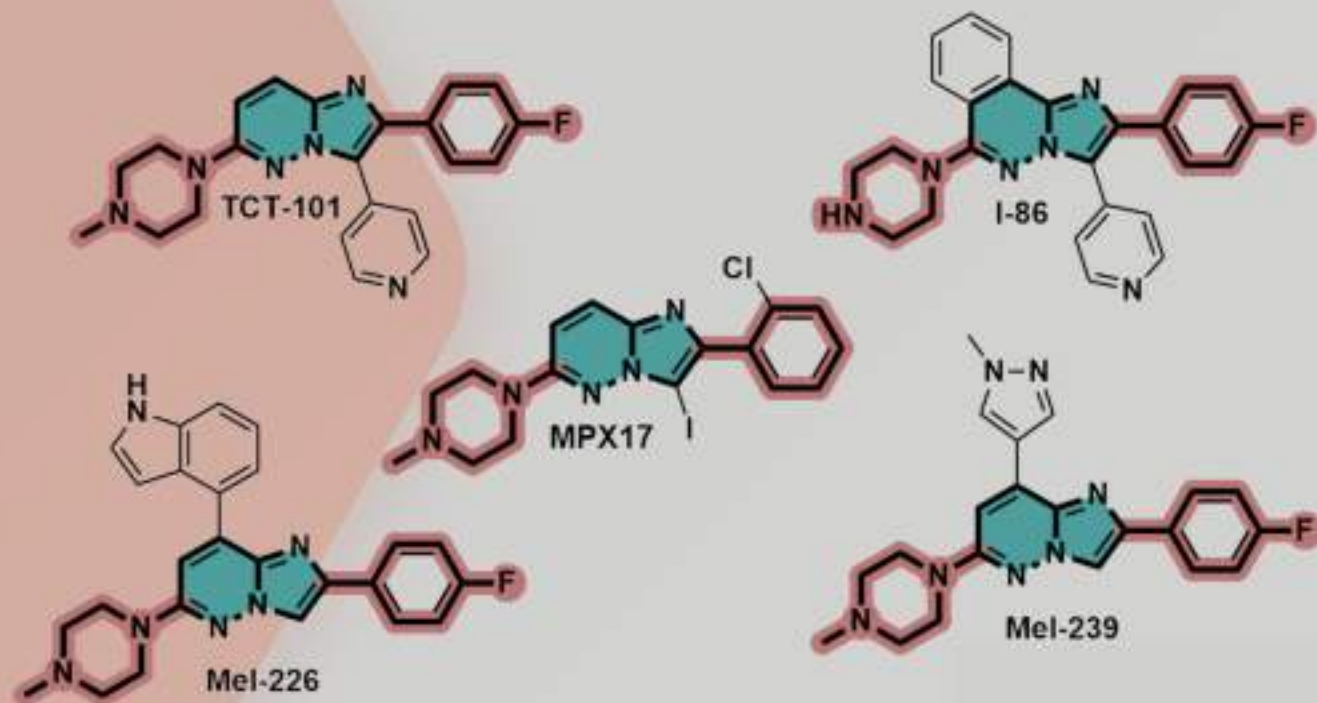
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VS



Madurella mycetoatis
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5 Hits

Methodology



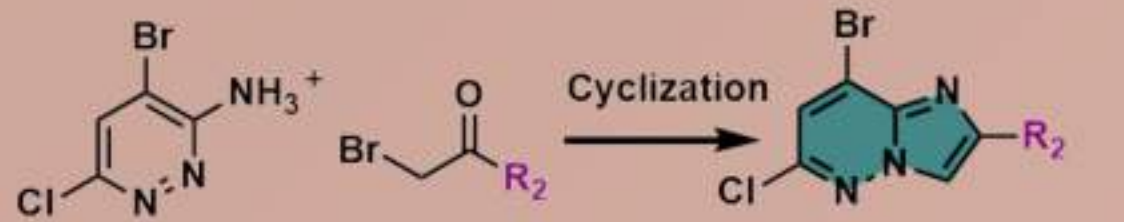
**Phenotypic
screening
for hits**

Methodology

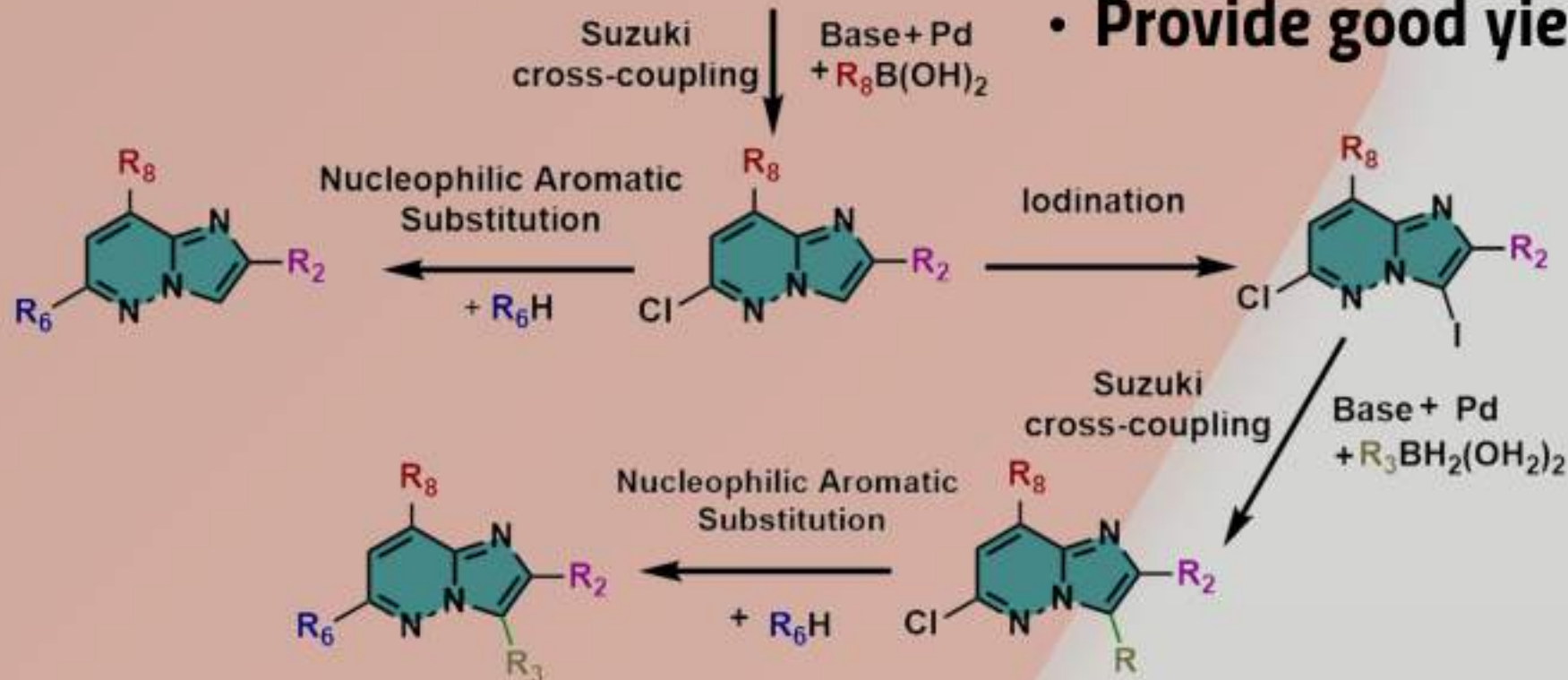
**Phenotypic
screening
for hits**

**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

**Phenotypic
screening
for hits**

**Hits library
expansion**

Cytotoxicity

Basal Cytotoxicity



NIH-3T3 Fibroblasts

**Our products
VS
Itraconazole and AmB**

MTT viability Assay

Methodology

**Phenotypic
screening
for hits**

**Hits library
expansion**

Cytotoxicity

Methodology



SwissADME prediction Tool

www.nature.com/scientificreports

SCIENTIFIC REPORTS

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

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Antoine Daina¹, Olivier Michielin^{1,2,3} & Vincent Zoete¹

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

Methodology



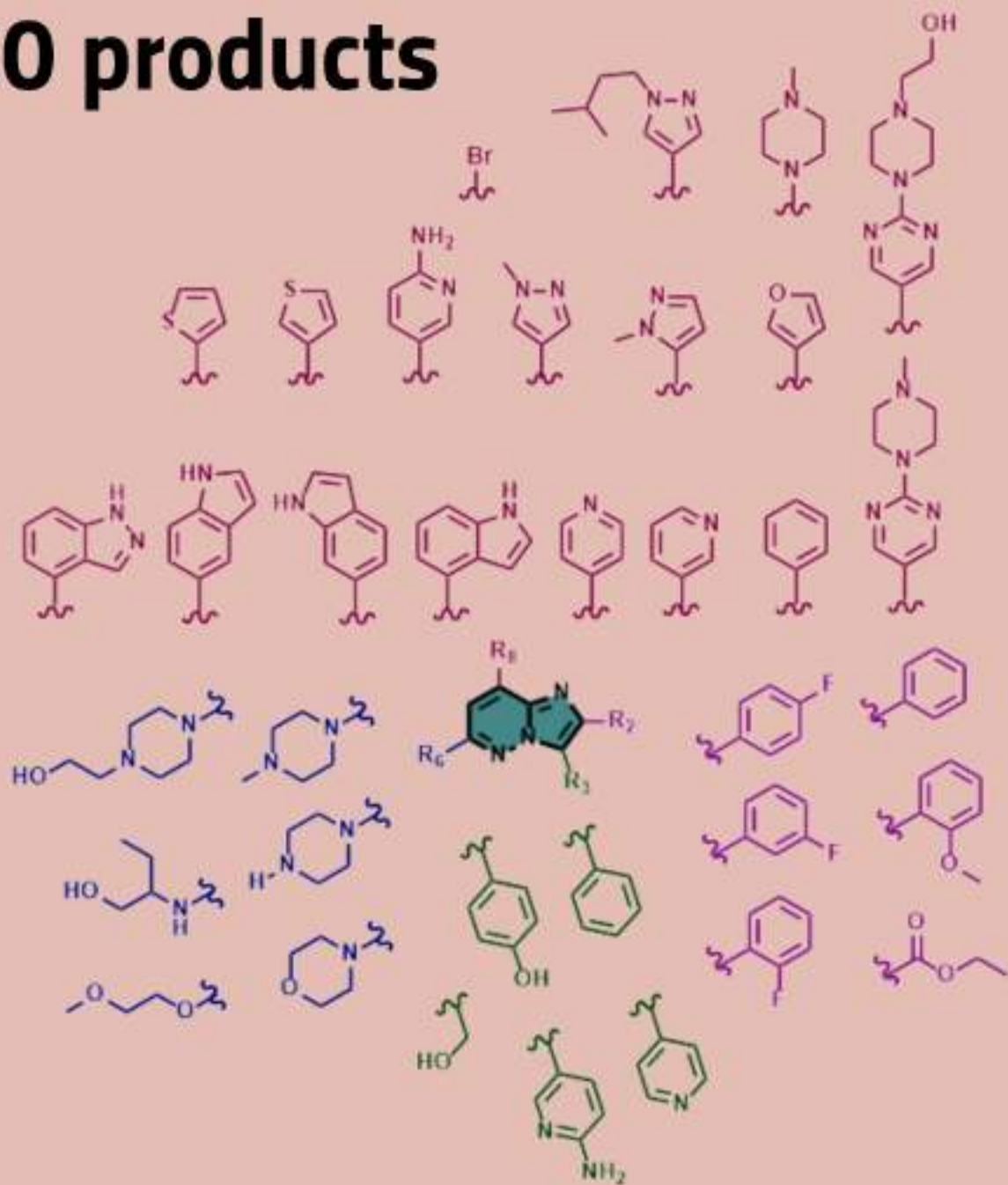


Results

Results

**Synthesized
products**

60 products



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

Results

**Synthesized
products**

Results

**Synthesized
products**

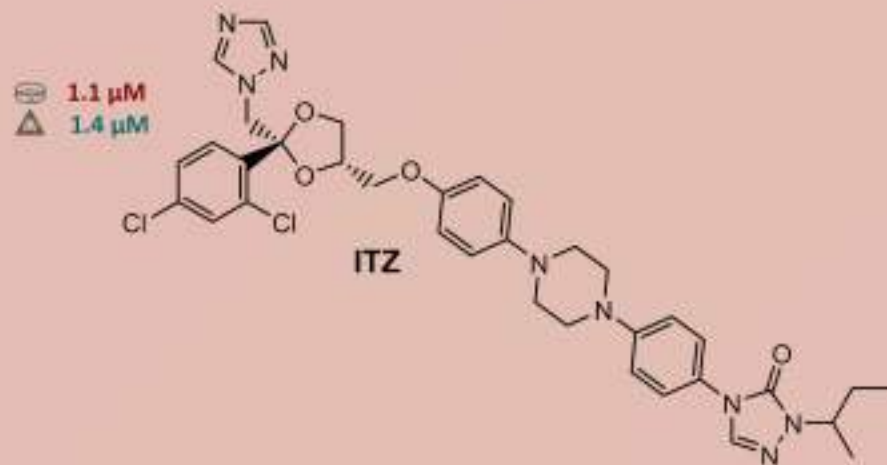
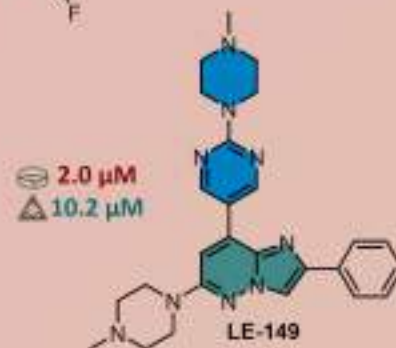
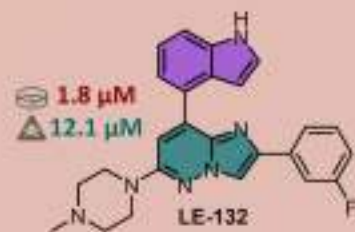
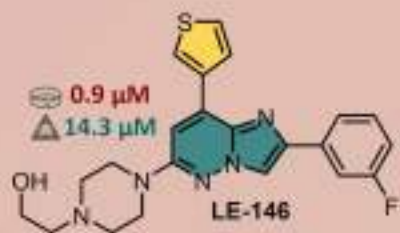
The diagram consists of two light orange hexagonal nodes with rounded corners. The first node, on the left, contains the text 'Synthesized products'. The second node, on the right, contains the text 'Activity and Cytotoxicity'. The two nodes are connected by a dark blue diagonal line that runs from the top-right corner of the first node to the bottom-left corner of the second node. The background is split diagonally from the top-left to the bottom-right, with a light gray area on the left and a dark blue area on the right.

**Activity and
Cytotoxicity**

IC50s (Efficacy vs Toxicity)

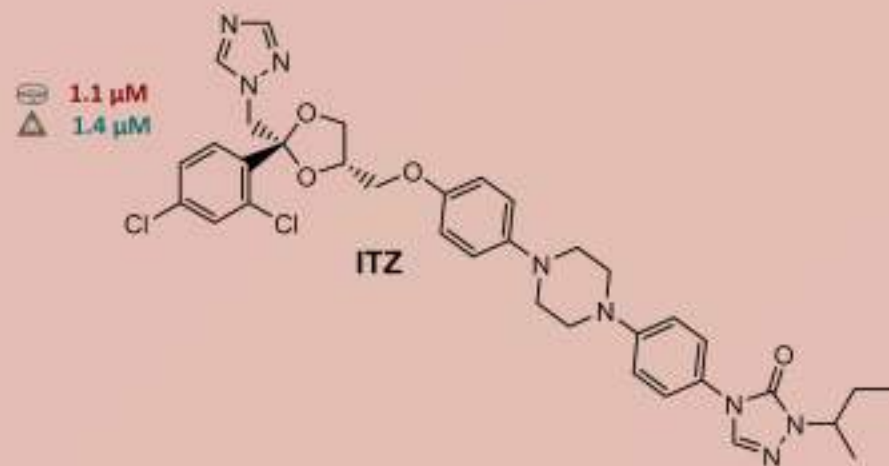
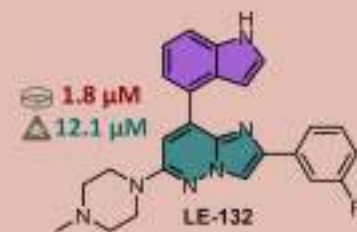
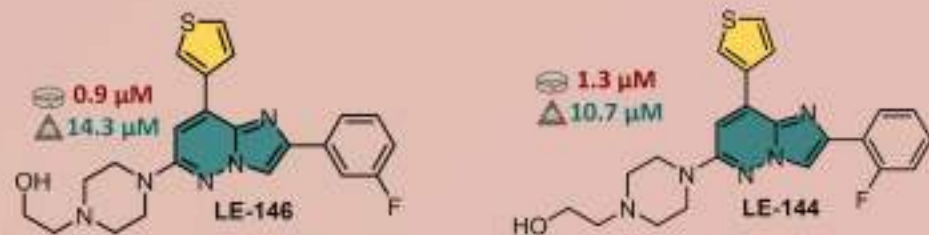
IC50s (Efficacy vs Toxicity)

- 5 products had an $IC_{50} \leq 2 \mu M$ with 1 product **LE-146** with an IC_{50} of **0.9 μM** (less than ITZ, $IC_{50} = 1.1 \mu M$)



IC50s (Efficacy vs Toxicity)

- 5 products had an **IC50 \leq 2 μ M** with 1 product **LE-146** with an **IC50 of 0.9 μ M** (less than ITZ, IC50 = 1.1 μ M)
- All of 5 products had **significantly less toxicity compared to itraconazole** against fibroblasts .
- Much **simpler structure** compared to ITZ

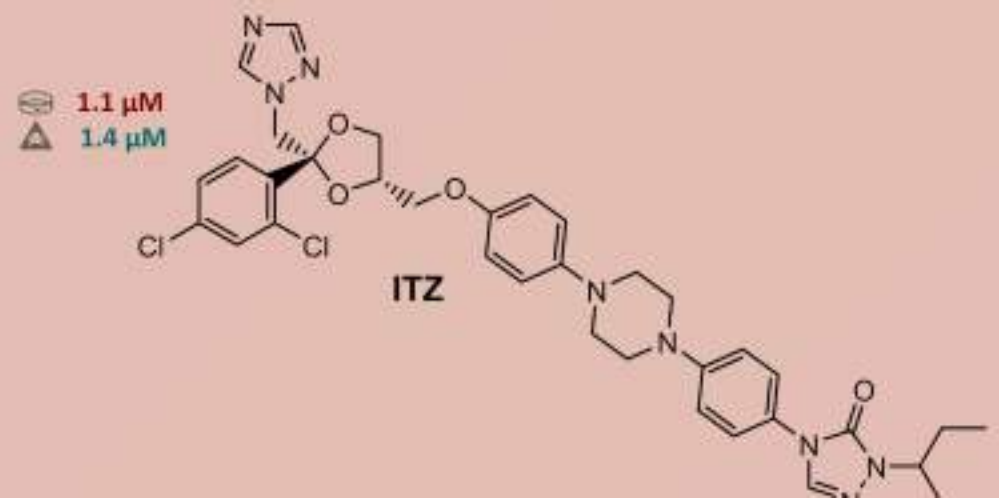
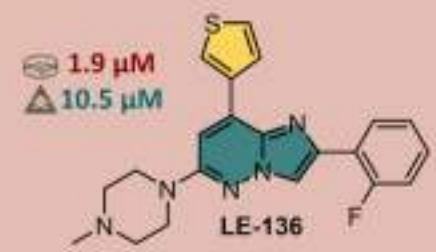
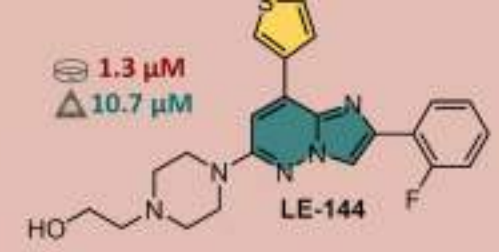
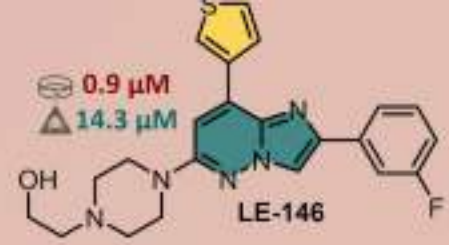


(vs Toxicity)

$IC_{50} \leq 2 \mu M$ with 1
in IC_{50} of $0.9 \mu M$
($1.1 \mu M$)

significantly less
itraconazole against

compared to ITZ



Results

**Synthesized
products**

**Activity and
Cytotoxicity**

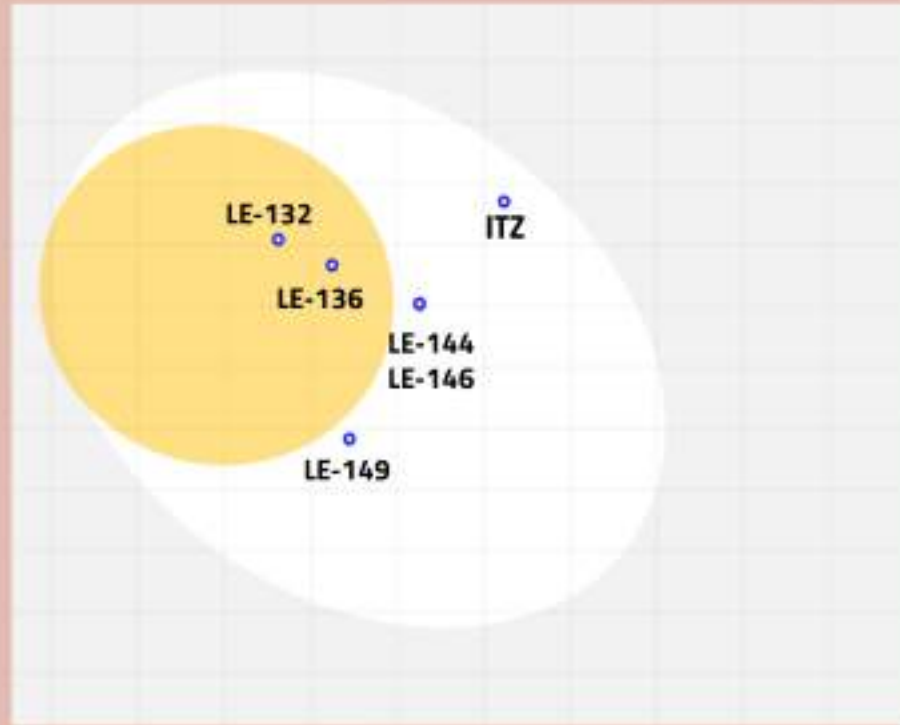
Results

**Synthesized
products**

**Activity and
Cytotoxicity**

**Predicted
Pharmaco-
kinetics**

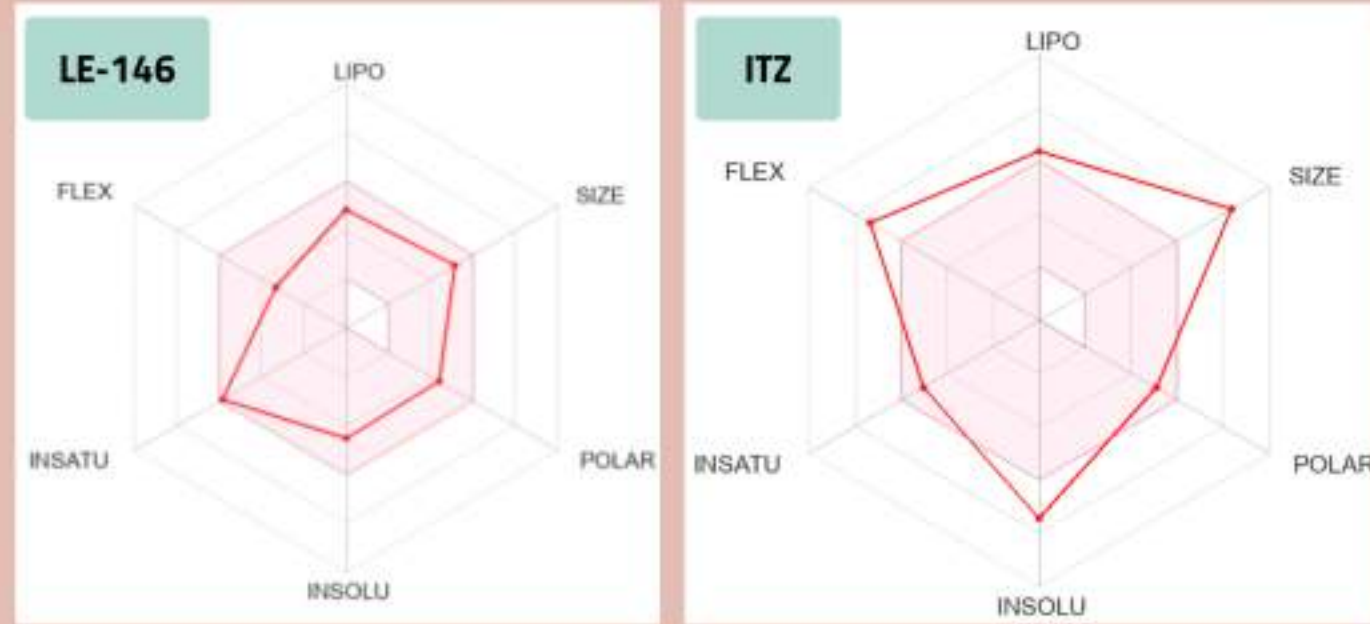
The Boiled Egg



- High probability of passive absorption by the GIT.
- High probability of brain penetration.
- Non-substrate of P-gp.

- Actively effluxed by P-gp.

Bioavailability Radar



Optimal range for each physicochemical property

Lipophilicity

Size

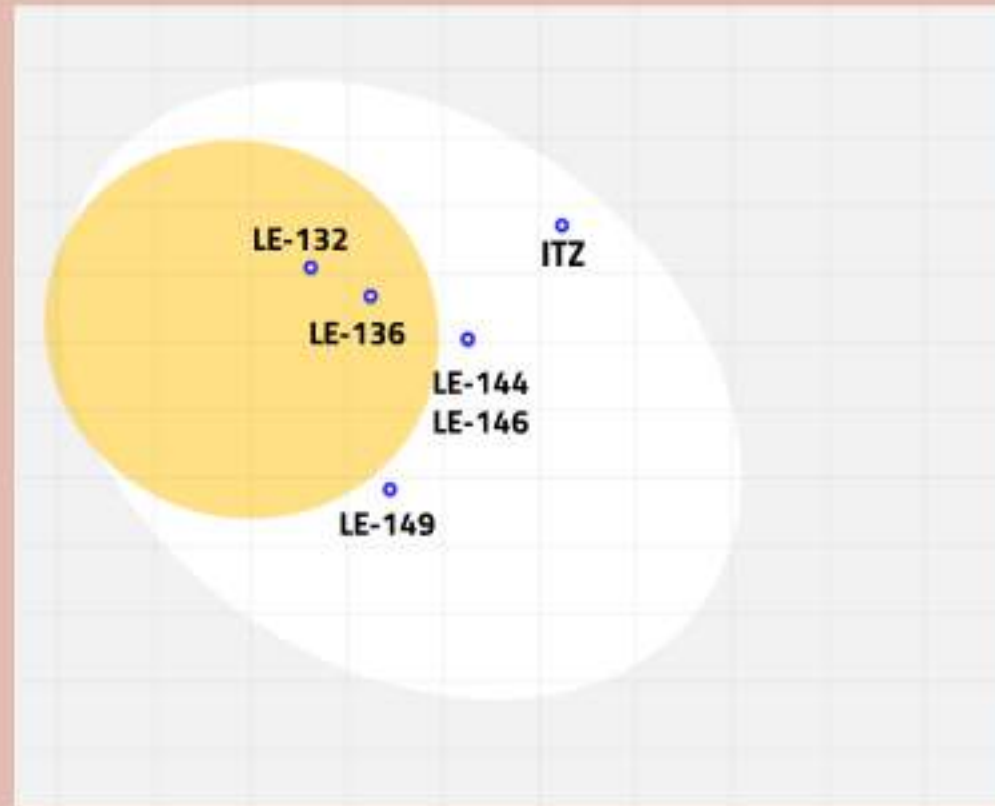
Polarity

Saturation

Flexibility

Solubility (log S)

The Boiled Egg



High probability of passive absorption by the GIT.



High probability of brain penetration.



Non-substrate of P-gp.



Actively effluxed by P-gp.

Bioavailab



Optimal range for e

Lipophilicity

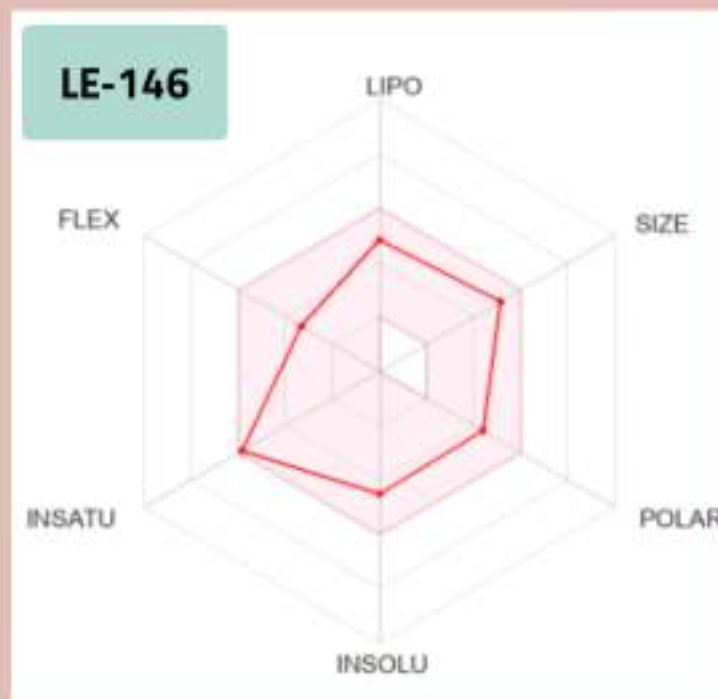
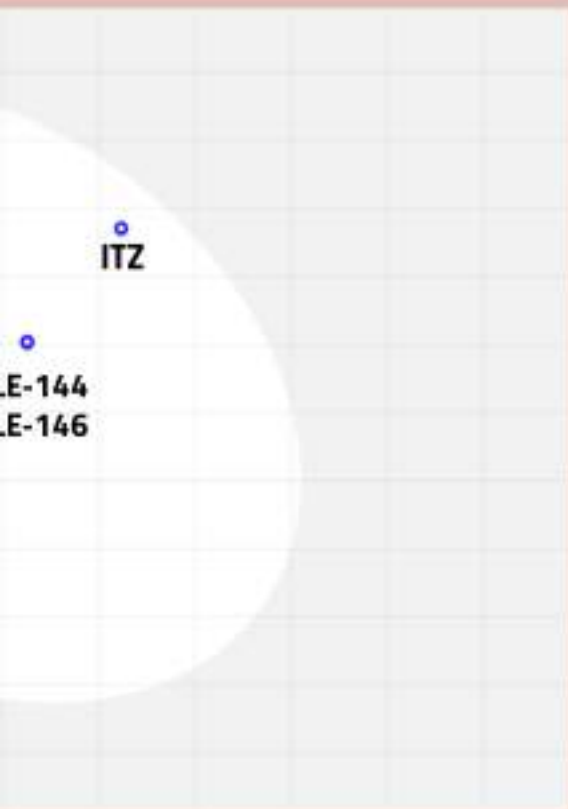
Size

Saturation

Flexi

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Lipophilicity

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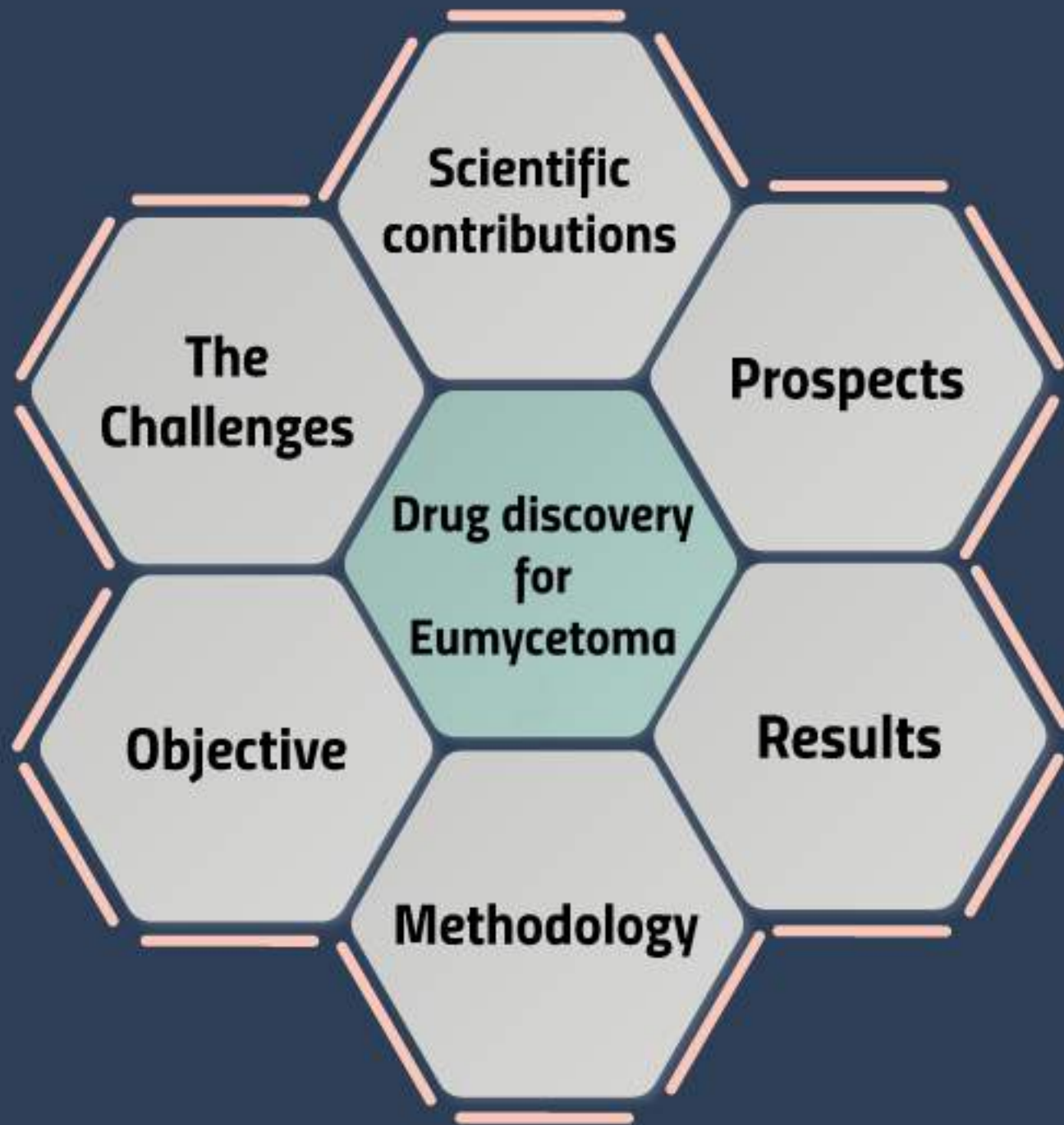
Solubility (log S)

Results

**Synthesized
products**

**Activity and
Cytotoxicity**

**Predicted
Pharmaco-
kinetics**







**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**

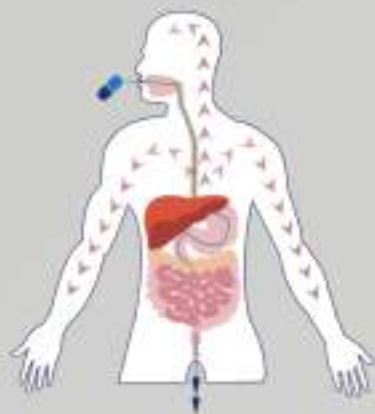
**More studies
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***In-vivo* evaluation using
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**Proteomics and
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**Pharmacokinetics and
Pharmacodynamics studies**

**More studies
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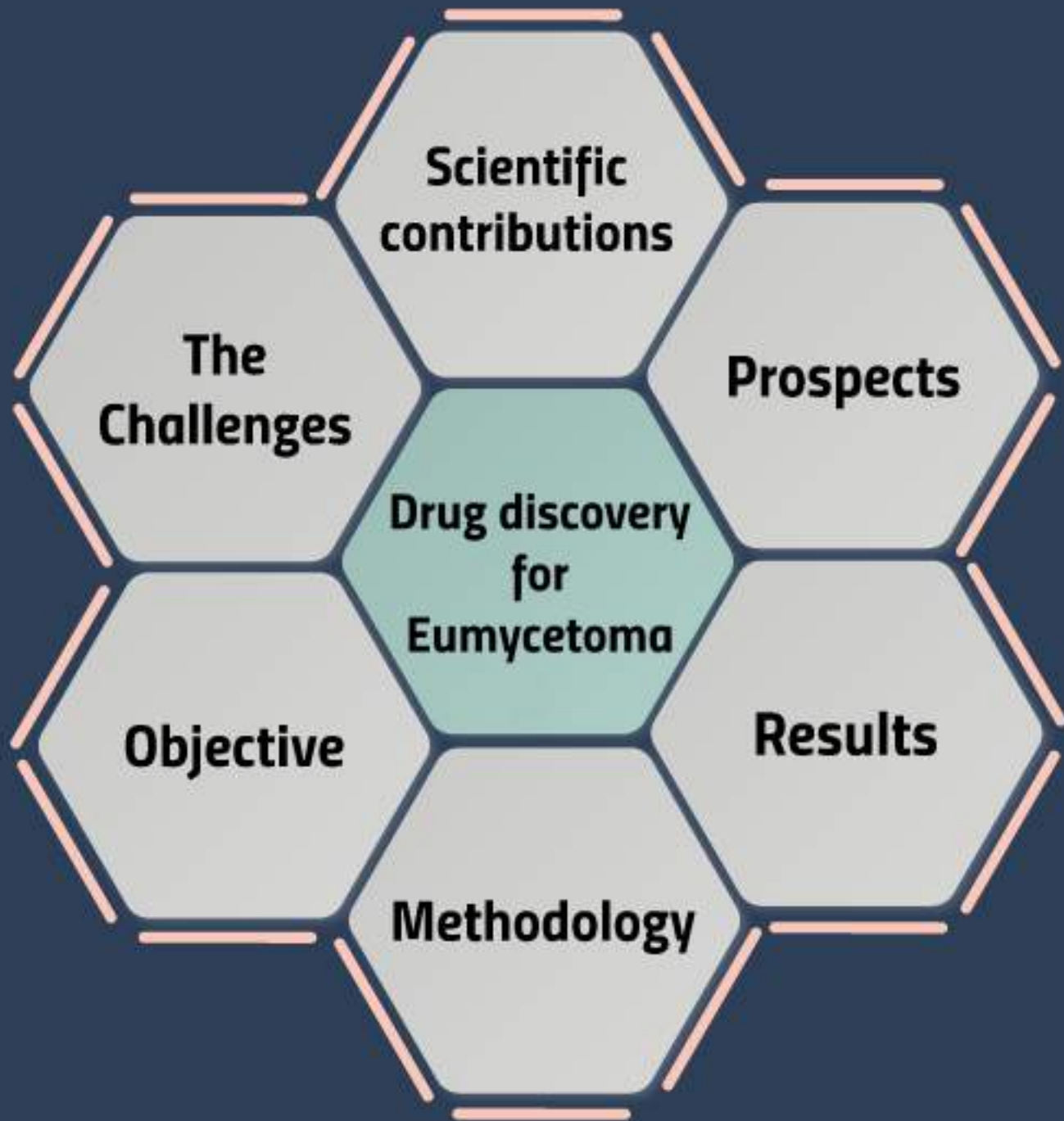


**Pharmacokinetics and
Pharmacodynamics studies**



**Computational studies
to design more potent
compounds**

**More studies
are needed**





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

Lamis Y. M. Elkheir^{1,2,3,4}, Rayan Haroun^{1,2,3,4}, Magdi Awadalla Mohamed^{1,2,3,4}, Ahmed Hassan Fahal^{1,2,3,4}

¹ The Egyptian Research Center for Studies of Medicines, Helwan, Egypt
² Department of Medicinal Chemistry, Faculty of Pharmacy, Helwan University, Helwan, Egypt
³ Faculty of Pharmacy, Helwan University, Helwan, Egypt
⁴ National Scientific Research Center, Helwan, Egypt

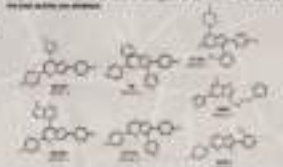
ABSTRACT

Eumycetoma is a rare disease caused by the growth of fungi in the skin, leading to tissue destruction and deformities. The main cause is the infection of the skin by the fungus *Madurella mycetomatis*, which is a prime causative agent of Eumycetoma. The disease is characterized by the formation of a mass of granules, known as a "grain", which is a collection of fungal hyphae and host cells. The disease is a chronic infection that can last for years and can be fatal if left untreated. The disease is a neglected tropical disease (NTD) and is a major cause of disability and poverty in developing countries. The disease is a major cause of disability and poverty in developing countries. The disease is a major cause of disability and poverty in developing countries.

INTRODUCTION

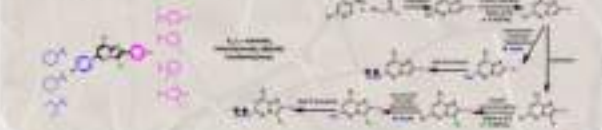
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Compound	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
1	1.2	1.5	1.8	2.1
2	1.5	1.8	2.1	2.4
3	1.8	2.1	2.4	2.7
4	2.1	2.4	2.7	3.0
5	2.4	2.7	3.0	3.3
6	2.7	3.0	3.3	3.6
7	3.0	3.3	3.6	3.9
8	3.3	3.6	3.9	4.2
9	3.6	3.9	4.2	4.5
10	3.9	4.2	4.5	4.8
11	4.2	4.5	4.8	5.1
12	4.5	4.8	5.1	5.4
13	4.8	5.1	5.4	5.7
14	5.1	5.4	5.7	6.0
15	5.4	5.7	6.0	6.3
16	5.7	6.0	6.3	6.6
17	6.0	6.3	6.6	6.9
18	6.3	6.6	6.9	7.2
19	6.6	6.9	7.2	7.5
20	6.9	7.2	7.5	7.8
21	7.2	7.5	7.8	8.1
22	7.5	7.8	8.1	8.4
23	7.8	8.1	8.4	8.7
24	8.1	8.4	8.7	9.0
25	8.4	8.7	9.0	9.3
26	8.7	9.0	9.3	9.6
27	9.0	9.3	9.6	9.9
28	9.3	9.6	9.9	10.2
29	9.6	9.9	10.2	10.5
30	9.9	10.2	10.5	10.8
31	10.2	10.5	10.8	11.1
32	10.5	10.8	11.1	11.4
33	10.8	11.1	11.4	11.7
34	11.1	11.4	11.7	12.0
35	11.4	11.7	12.0	12.3
36	11.7	12.0	12.3	12.6
37	12.0	12.3	12.6	12.9
38	12.3	12.6	12.9	13.2
39	12.6	12.9	13.2	13.5
40	12.9	13.2	13.5	13.8
41	13.2	13.5	13.8	14.1
42	13.5	13.8	14.1	14.4
43	13.8	14.1	14.4	14.7
44	14.1	14.4	14.7	15.0
45	14.4	14.7	15.0	15.3
46	14.7	15.0	15.3	15.6
47	15.0	15.3	15.6	15.9
48	15.3	15.6	15.9	16.2
49	15.6	15.9	16.2	16.5
50	15.9	16.2	16.5	16.8



RESULTS AND DISCUSSION

The results of the study show that the synthesized compounds are active against *Madurella mycetomatis*. The compounds were tested against the fungus in a 96-well microtiter plate. The results showed that the compounds were active against the fungus in a concentration-dependent manner. The compounds were active against the fungus in a concentration-dependent manner. The compounds were active against the fungus in a concentration-dependent manner.



CONCLUSION

The study concludes that the synthesized compounds are active against *Madurella mycetomatis*. The compounds were tested against the fungus in a 96-well microtiter plate. The results showed that the compounds were active against the fungus in a concentration-dependent manner. The compounds were active against the fungus in a concentration-dependent manner. The compounds were active against the fungus in a concentration-dependent manner.

Design and synthesis of a novel series of imidazo[1,2-b]pyridazines as antitubercular agents against *Mycobacterium tuberculosis*, the prime causative agent of Tuberculosis

Lamis Y. M. Elkheir^{1,2,3,4}, Rayan Haroun^{1,2,3,4}, Magdi Awadalla Mohamed^{1,2,3,4}, Ahmed Hassan Fahal^{1,2,3,4}

¹ The Egyptian Research Center for Studies of Medicines, Helwan, Egypt
² Department of Medicinal Chemistry, Faculty of Pharmacy, Helwan University, Helwan, Egypt
³ Faculty of Pharmacy, Helwan University, Helwan, Egypt
⁴ National Scientific Research Center, Helwan, Egypt

ABSTRACT

Tuberculosis is a infectious lung disease that leads to tissue destruction and deformities. The main cause is the infection of the lung by the bacterium *Mycobacterium tuberculosis*, which is a prime causative agent of Tuberculosis. The disease is characterized by the formation of a mass of granules, known as a "grain", which is a collection of bacterial cells and host cells. The disease is a chronic infection that can last for years and can be fatal if left untreated. The disease is a neglected tropical disease (NTD) and is a major cause of disability and poverty in developing countries. The disease is a major cause of disability and poverty in developing countries. The disease is a major cause of disability and poverty in developing countries.

INTRODUCTION

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RESULTS AND DISCUSSION

The results of the study show that the synthesized compounds are active against *Mycobacterium tuberculosis*. The compounds were tested against the bacterium in a 96-well microtiter plate. The results showed that the compounds were active against the bacterium in a concentration-dependent manner. The compounds were active against the bacterium in a concentration-dependent manner. The compounds were active against the bacterium in a concentration-dependent manner.

CONCLUSION

The study concludes that the synthesized compounds are active against *Mycobacterium tuberculosis*. The compounds were tested against the bacterium in a 96-well microtiter plate. The results showed that the compounds were active against the bacterium in a concentration-dependent manner. The compounds were active against the bacterium in a concentration-dependent manner. The compounds were active against the bacterium in a concentration-dependent manner.



PLOS NEGLECTED TROPICAL DISEASES

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REVIEW

Madurella mycetomatis causing eumycetoma medical treatment: The challenges and prospects

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

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

Lamis Y.M. Elkheir^{a,b}, Rayan Haroun^a, Magdi Awadalla Mohamed^a, Ahmed Hassan Fahal^a

^a The Egyptian Research Center for Diagnosis of Mycetozoa Infections, Faculty of Pharmacy, University of Assiut, Assiut, Egypt; ^b Faculty of Pharmacy, University of Assiut, Assiut, Egypt; ^c Faculty of Pharmacy, University of Assiut, Assiut, Egypt; ^d Faculty of Pharmacy, University of Assiut, Assiut, Egypt

ABSTRACT
Eumycetoma is a rare but serious disease caused by the growth of fungi in the skin and soft tissues. It is characterized by the formation of a mass of granules, abscesses, and sinus tracts. The disease is caused by the invasion of the skin by various fungi, including *Madurella mycetomatis*, which is the most common causative agent. The disease is often neglected, and there is a need for novel and effective treatments. In this study, we designed and synthesized a series of novel heterocyclic compounds and evaluated their antifungal activity against *M. mycetomatis*. The results showed that several compounds exhibited significant antifungal activity, with some showing a higher degree of inhibition than the standard drug, itraconazole. The most active compound was 1-(2-(4-(2-(2,2,2-trifluoroethyl)-1H-imidazo[1,2-b]pyridazin-5-yl)phenoxy)ethyl)pyrrolidine (10), which showed a 100% inhibition of *M. mycetomatis* growth at a concentration of 100 µg/ml. The results of this study suggest that the designed compounds may be promising candidates for the treatment of eumycetoma.

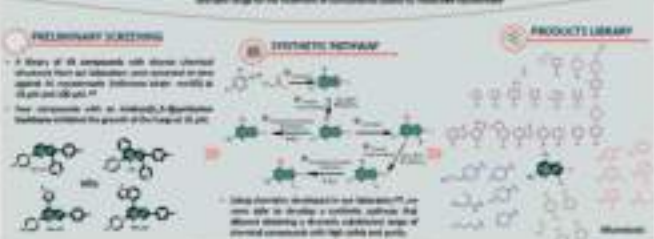


CONCLUSION
The results of this study suggest that the designed compounds may be promising candidates for the treatment of eumycetoma. Further studies are needed to evaluate the safety and efficacy of these compounds in clinical trials.

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

Lamis Y.M. Elkheir^{a,b}, Rayan Haroun^a, Wendy van de Sande^c, Pierre Besson^f, Magdi Awadalla Mohamed^a, Sébastien Roger^g, Ahmed Hassan Fahal^a, Cécile Enguehard-Gueffier^c

ABSTRACT
Eumycetoma is a neglected tropical disease that leads to tissue destruction and disability. It is caused by the growth of fungi in the skin and soft tissues. The disease is often neglected, and there is a need for novel and effective treatments. In this study, we designed and synthesized a series of novel imidazo[1,2-b]pyridazine derivatives and evaluated their antifungal activity against *M. mycetomatis*. The results showed that several compounds exhibited significant antifungal activity, with some showing a higher degree of inhibition than the standard drug, itraconazole. The most active compound was 1-(2-(4-(2-(2,2,2-trifluoroethyl)-1H-imidazo[1,2-b]pyridazin-5-yl)phenoxy)ethyl)pyrrolidine (10), which showed a 100% inhibition of *M. mycetomatis* growth at a concentration of 100 µg/ml. The results of this study suggest that the designed compounds may be promising candidates for the treatment of eumycetoma.



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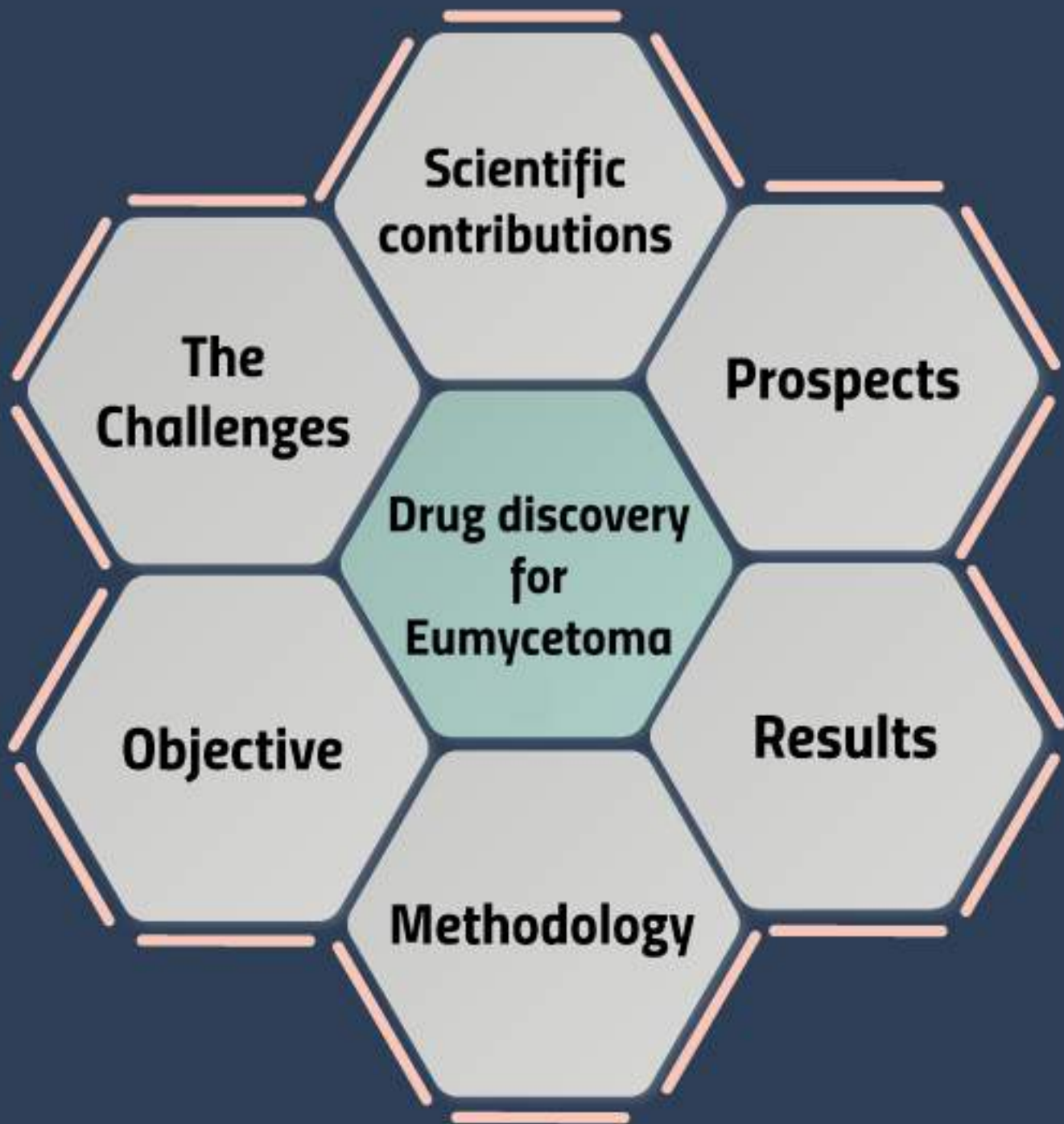
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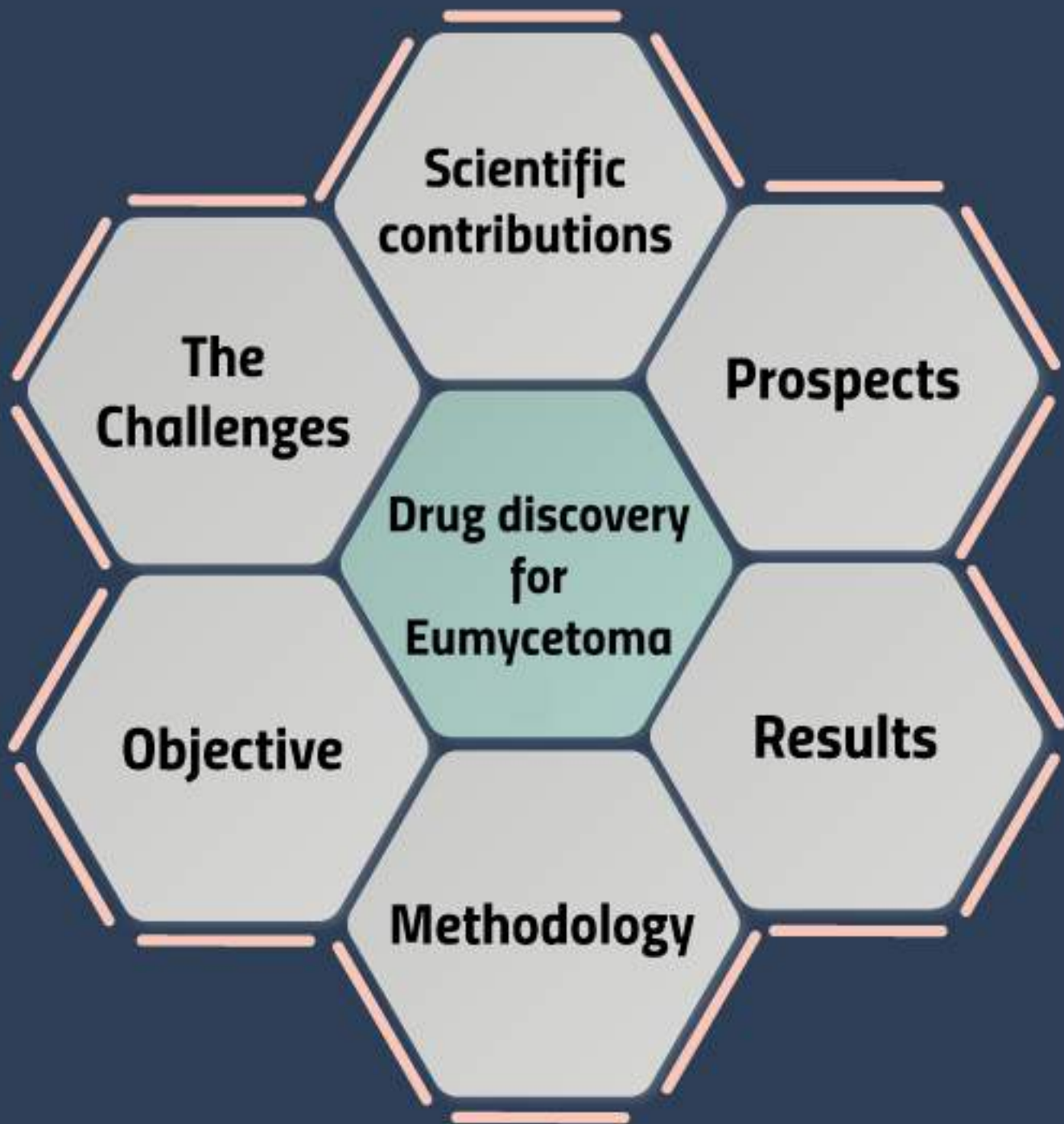


Emerging Therapeutics: The imidazo[1,2-b]pyridazine scaffold as a novel drug candidate for eumycetoma, a neglected tropical disease ☆

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 Desoubieux^g, Sébastien Roger^f, Wendy Wilhelmina Johanna van de Sande^d, Ahmed Hassan Fahal^a, Cécile Enguehard-Gueffier^c







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your kind
attention !**

