

SYNTHESES OF JUGLONE AND NAPHTHAZARIN NOVEL DERIVATIVES AND THEIR ANTIBACTERIAL ACTIVITIES

Valentin Duvauchelle

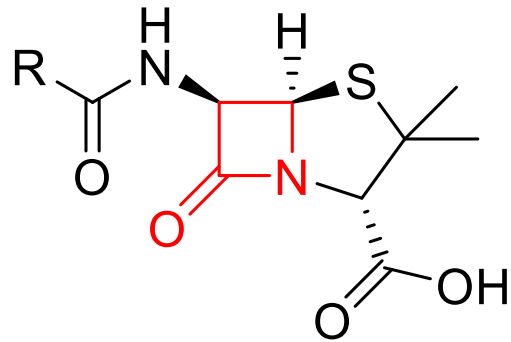
EA 7352 CHROME

Under supervision of Dr. Zohra Benfodda

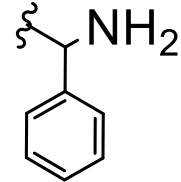
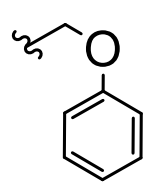
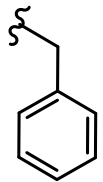
I-Introduction

What is an antibiotic?

Antibiotics are molecules that have the property of killing (**bactericidal**) or limiting the proliferation (**bacteriostatic**) of bacteria.



R =



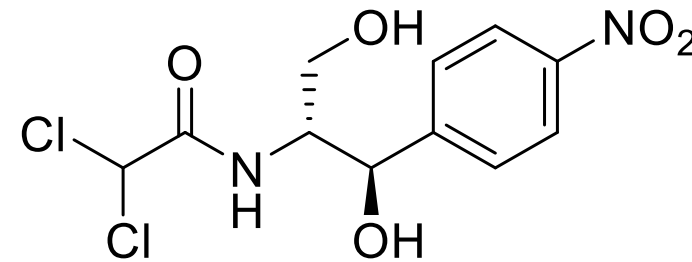
Penicillin

G

V

A

Bactericidal

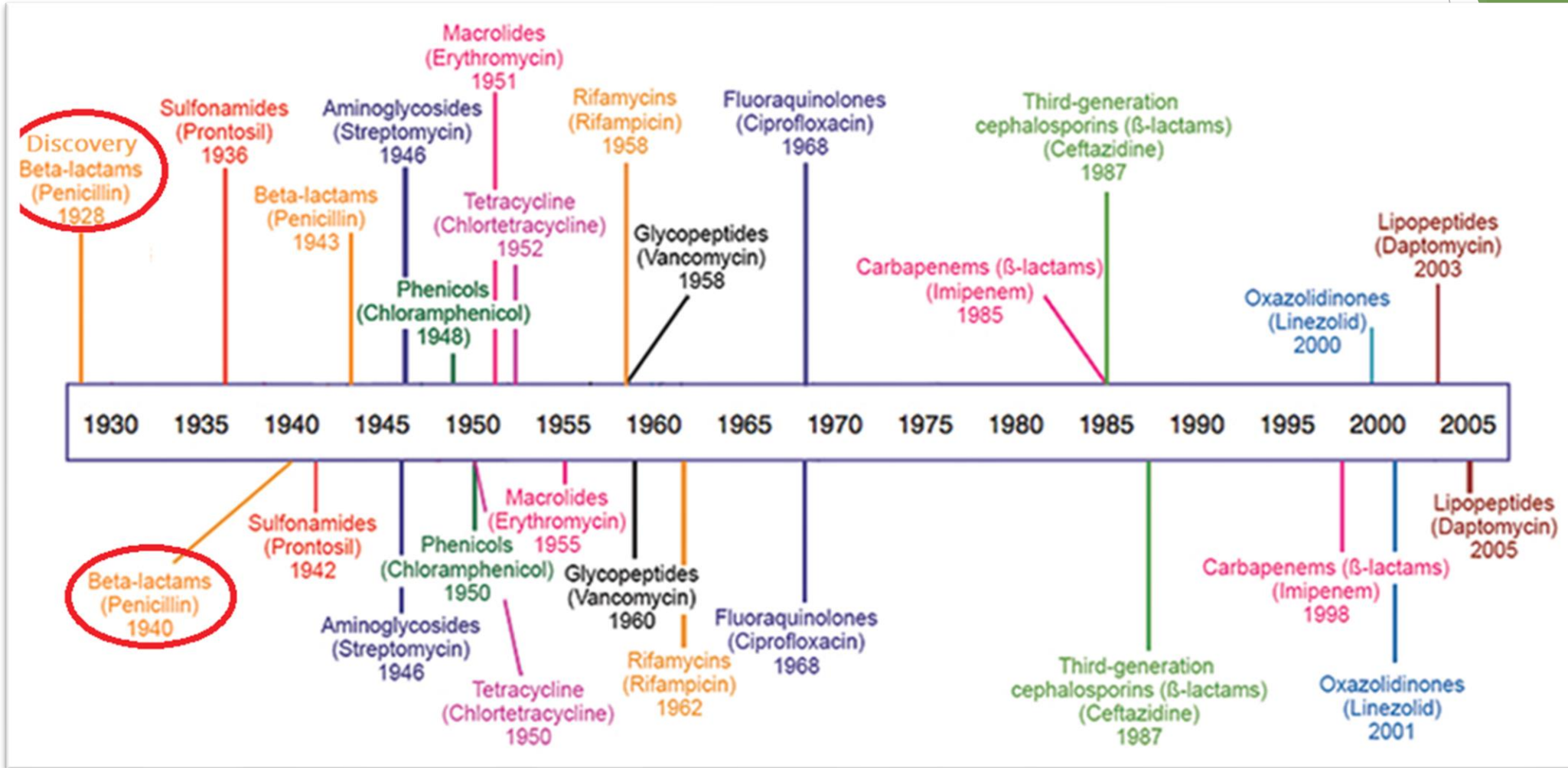


Chloramphenicol

Bacteriostatic

Resistances appearances

Year of antibiotic deployment

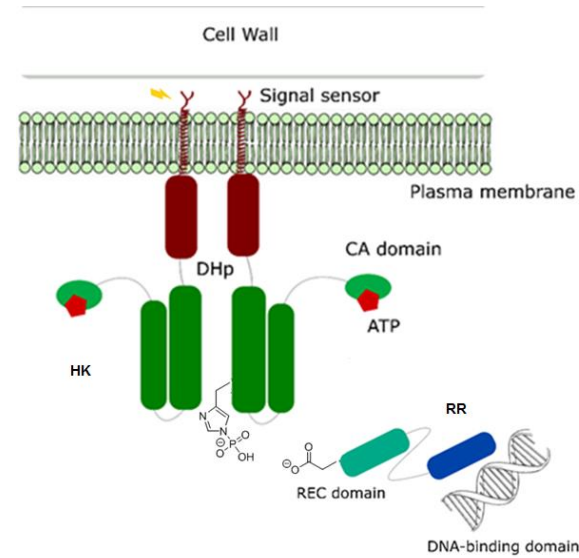


Year in which resistance was firstly discovered

Antibiotic resistance targets

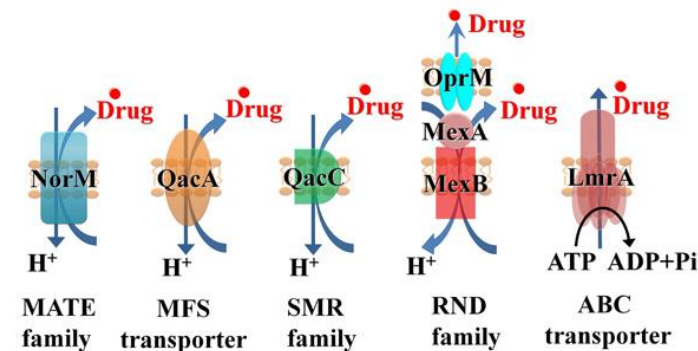
❖ Two-component systems (TCS)

- Histidine kinase (HK)
- Response regulator (RR)



❖ Efflux pumps

- Responsible for efflux of antibiotics

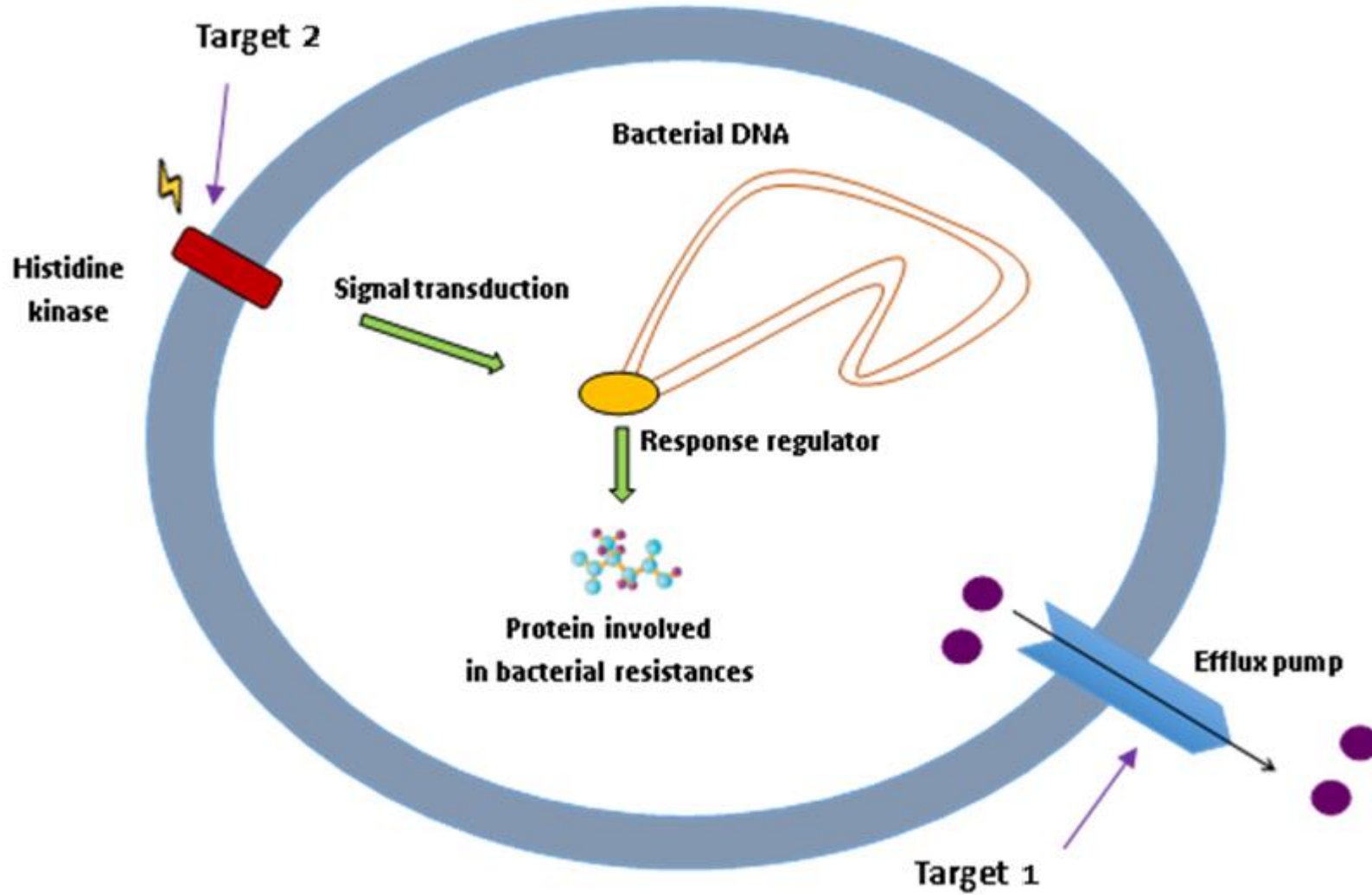


Bem *et al.* *ACS Chemical Biology*, **2015**, 10, 213-224

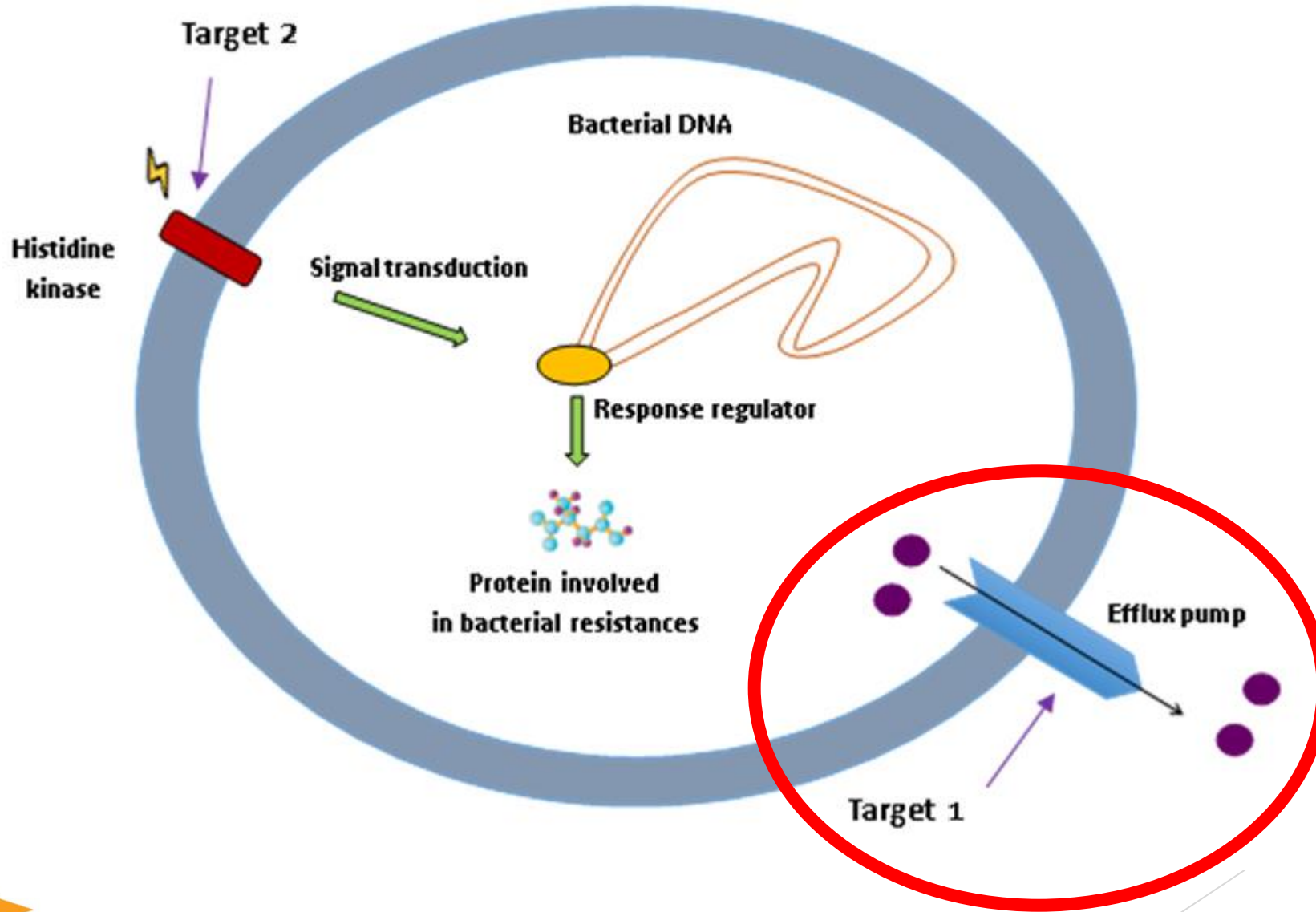
Alibert *et al.* *Expert Opinion on Drug Metabolism and Toxicology*, **2017**, 13, 301-309

Pagès *et al.* *Trends in Molecular Medicine*, **2005**, 11, 382-389

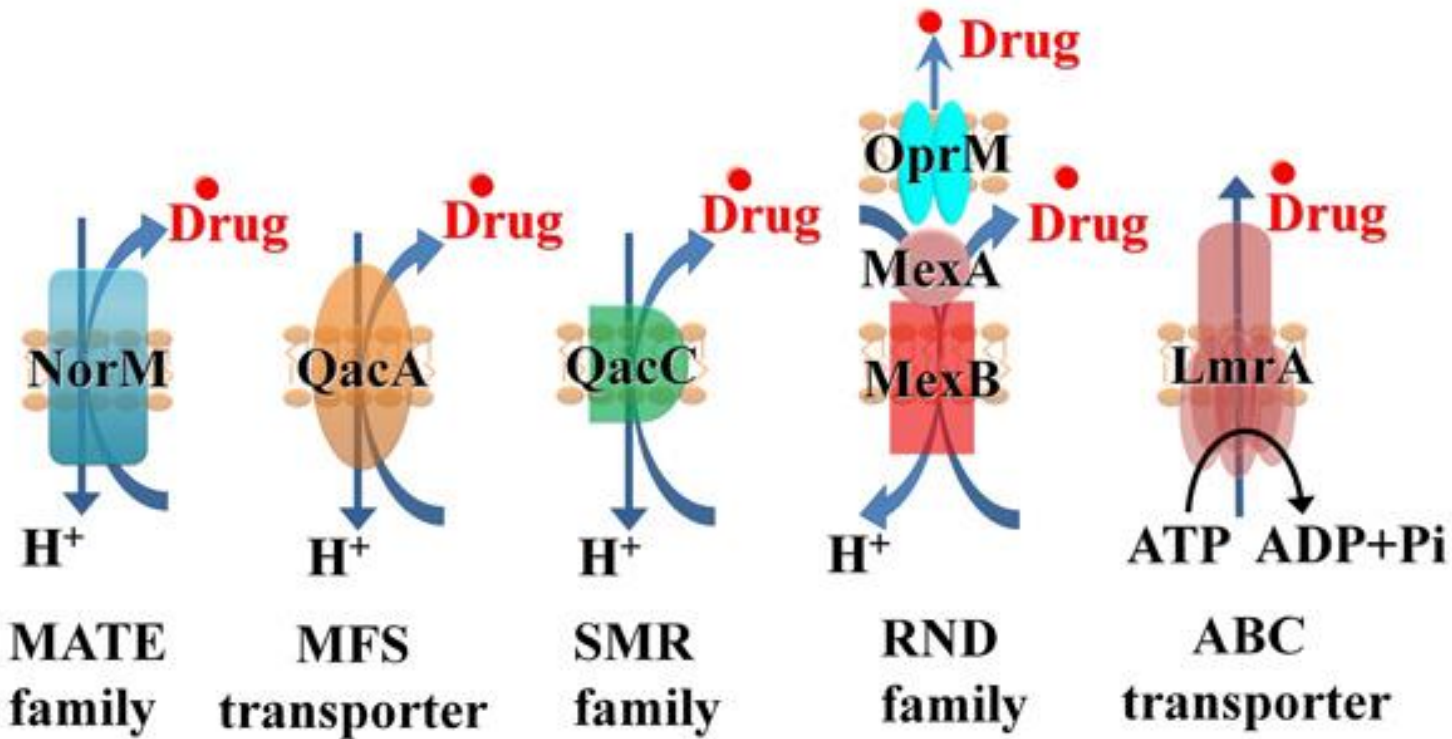
Antibiotic resistance targets



Antibiotic resistance targets



Target 1: efflux pumps



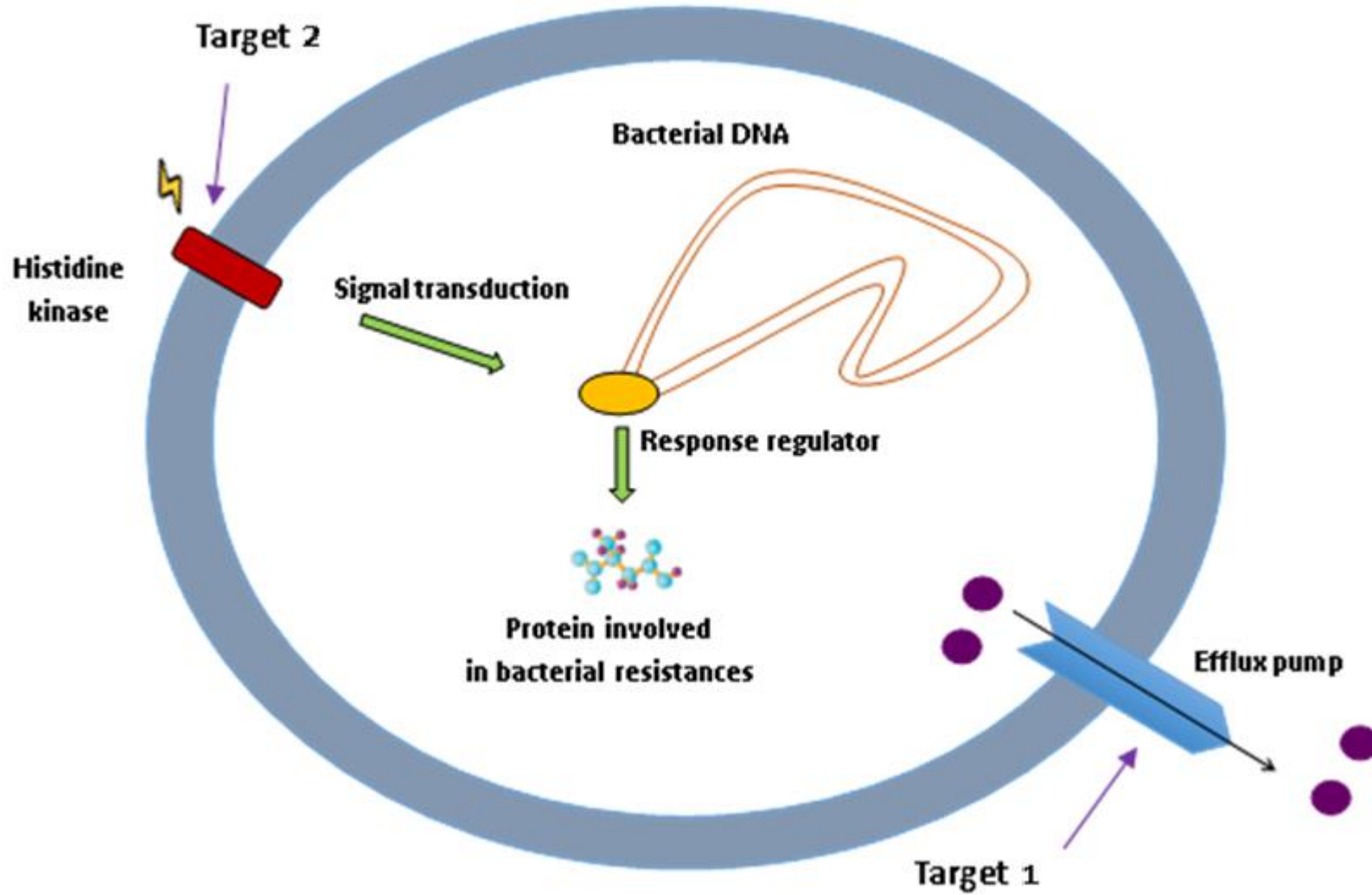
- Responsible for the efflux of metals, antibiotics and drugs
- Resistance to Tetracyclines & Fluoroquinolones
- Inherent for bacteria functioning

Alibert *et al.* *Curr Med Chem*, **2009**, 16, 301-317

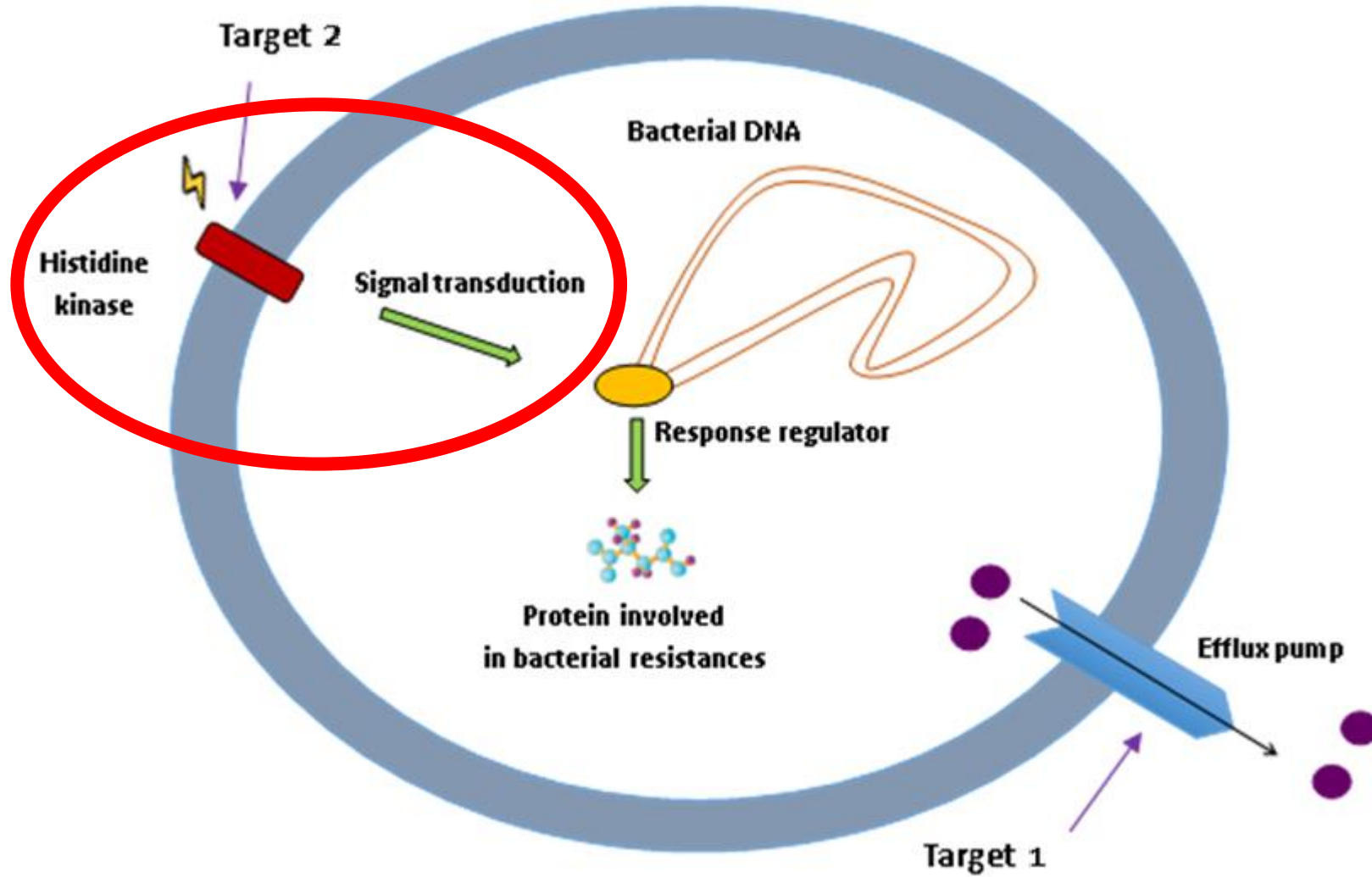
Alibert *et al.* *Expert Opinion on Drug Metabolism and Toxicology*, **2017**, 13, 301-309

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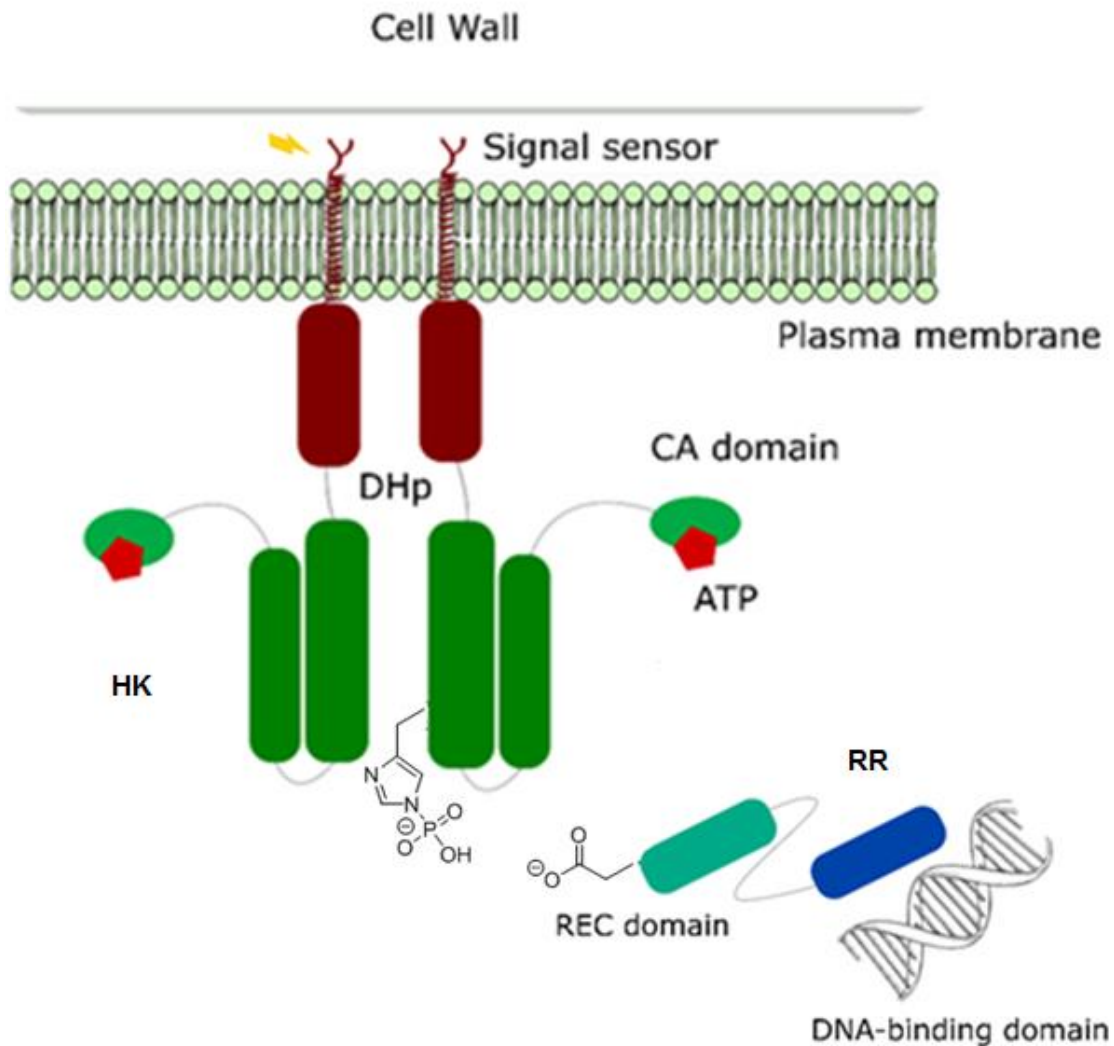
Antibiotic resistance targets



Antibiotic resistance targets



Target 2: two-component system

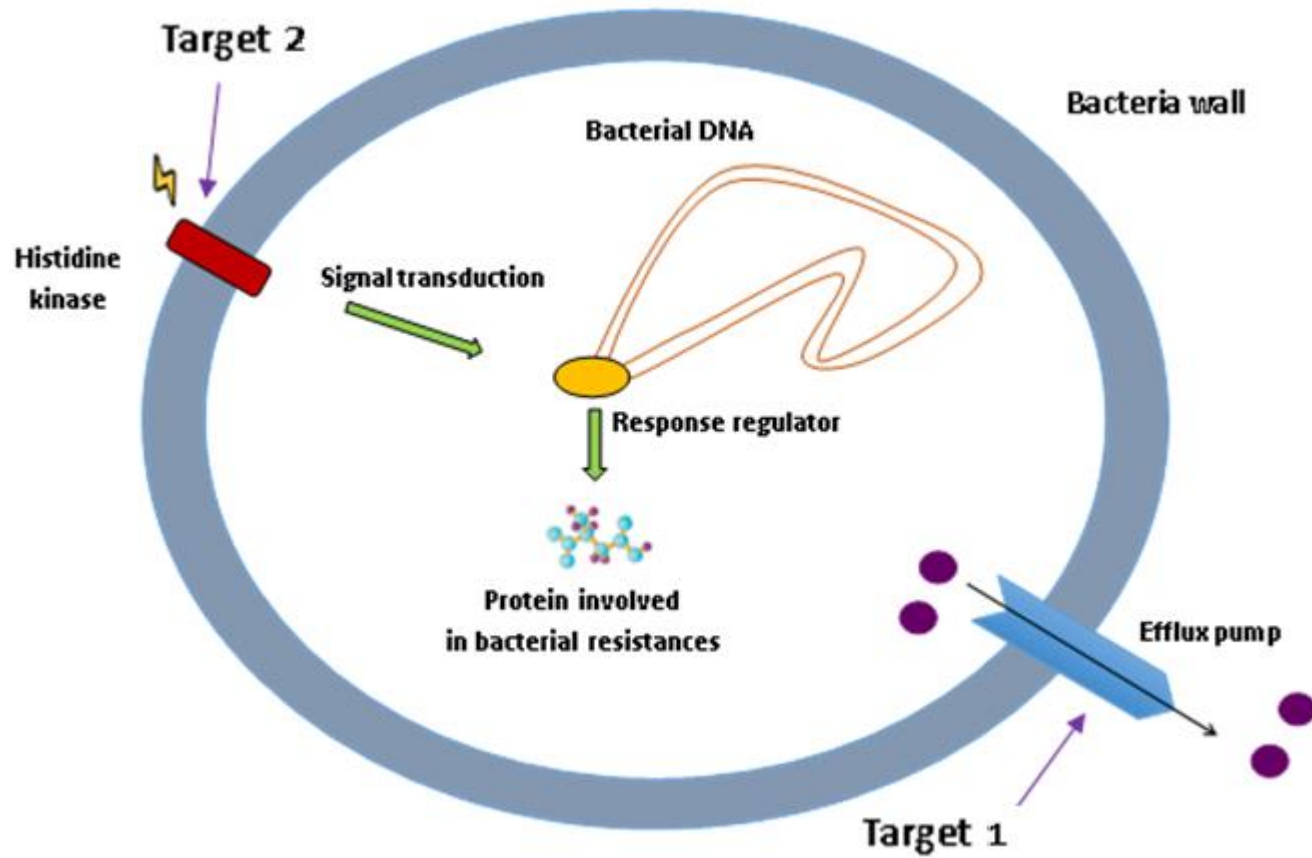


- HK & RR
- Involved in virulence, resistance phenomena and adaptation
- Ubiquitous in bacteria/absent in mammals
- Signal \Rightarrow His phosphorylation \Rightarrow Phosphotransfer



Transcription of genes involved in resistance phenomena.

Antibiotic resistance targets



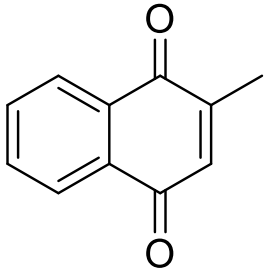
- Possibility to disrupt bacteria wall integrity
- Restore antibiotics activities
- Reduce bacterial resistances mechanisms

II-Syntheses & Results

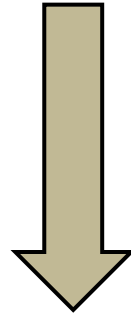
Derivatives conception

Menadione (vitamin K3) targets :

- efflux pumps
- histidine kinases
- bacterial membrane

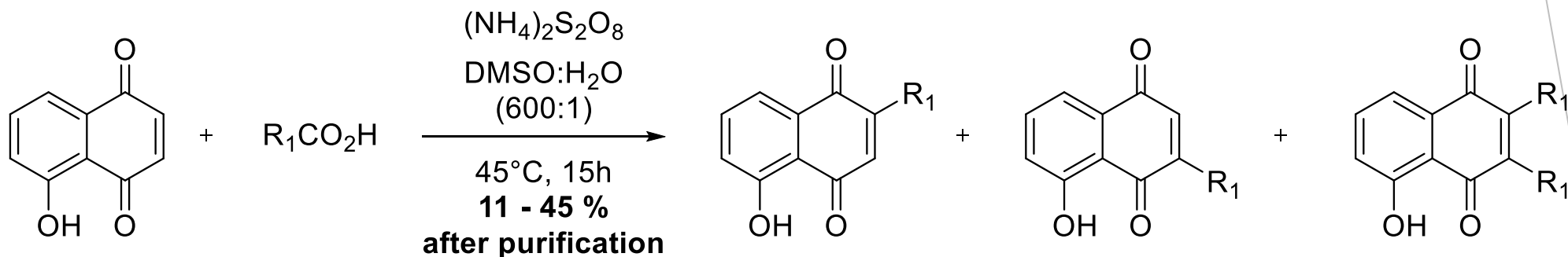


Menadione (Vitamin K3)



Design of series of compounds from a synthetic product analog of vitamin K.

Syntheses of juglone analogs



1
Juglone

R = *n*-hexyl
 R = *n*-heptyl
 R = *n*-octyl
 R = *n*-nonyl
 R = *n*-heptan-4-yl
 R = *sec*-butyl
 R = *tert*-pentyl
 R = neopentyl
 R = isobutyl
 R = 2-methylbutyl
 R = 2-butyl
 R = cyclohexyl

2a-2l

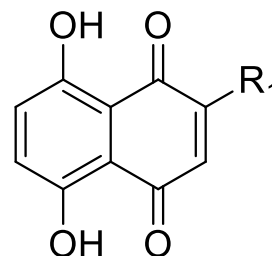
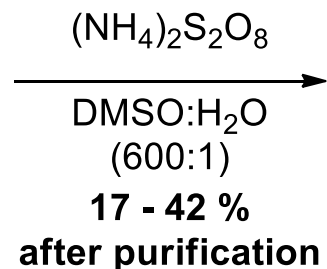
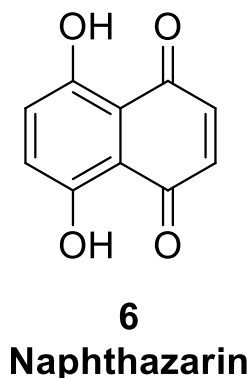
3a-3l
Major

4a-4l
Minor

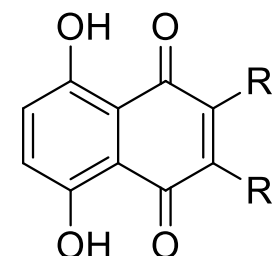
5a-5l
Very minor

30 juglone based new molecules have been synthesized following Minisci type reaction

Syntheses of naphthazarin analogs



8a-8l
Major



9a-9l
Minor

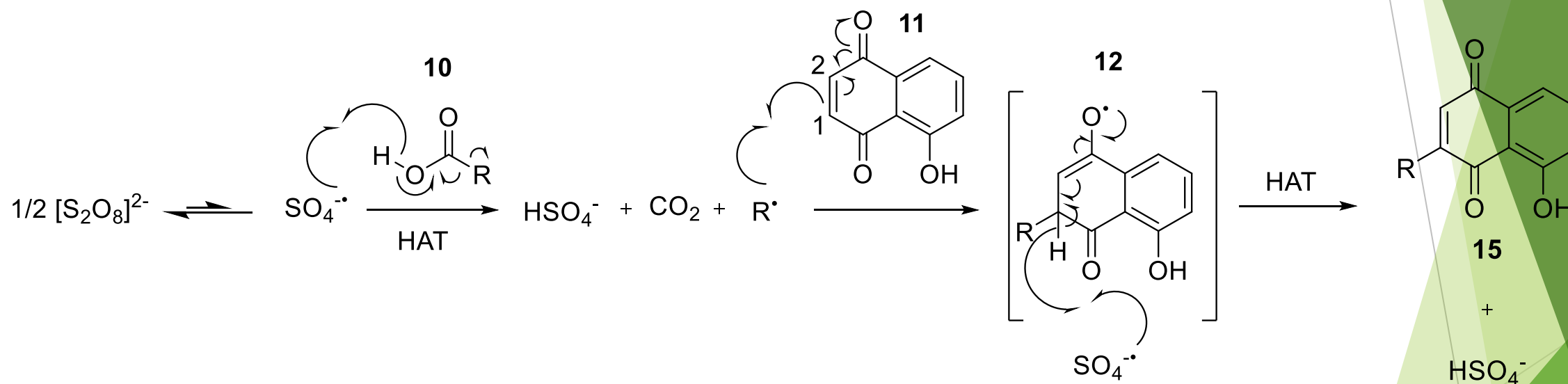
- R = *n*-hexyl
- R = *n*-heptyl
- R = *n*-octyl
- R = *n*-nonyl
- R = *n*-heptan-4-yl
- R = *sec*-butyl
- R = *tert*-pentyl
- R = neopentyl
- R = isobutyl
- R = 2-methylbutyl
- R = 2-butyl
- R = cyclohexyl

7a-7l

23 naphthazarin based new molecules have been synthesized following Minisci type reaction

Reaction mechanism

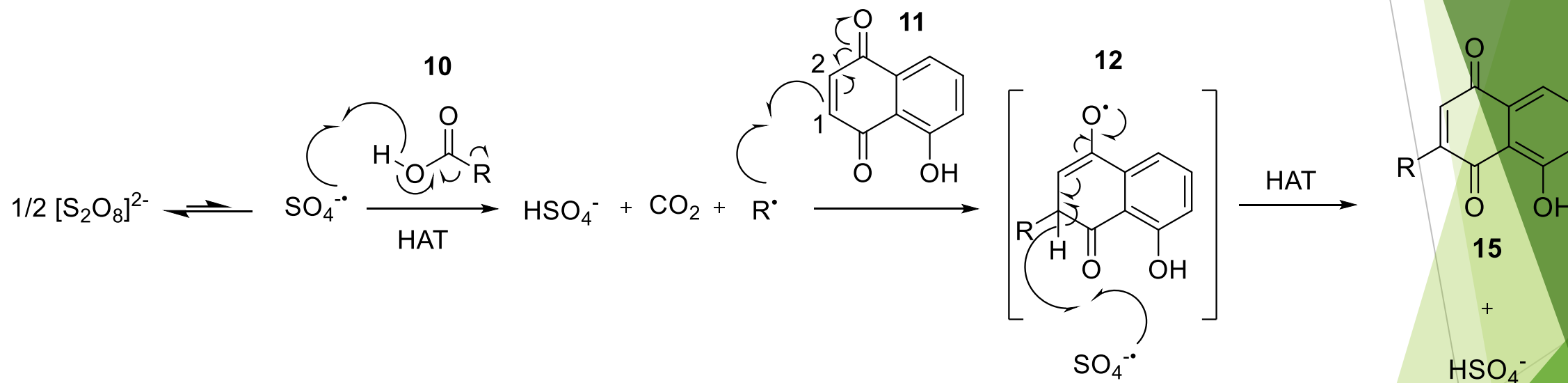
Minisci type reaction



- Radical reaction
- Formation of regioisomers

Reaction mechanism

Minisci type reaction



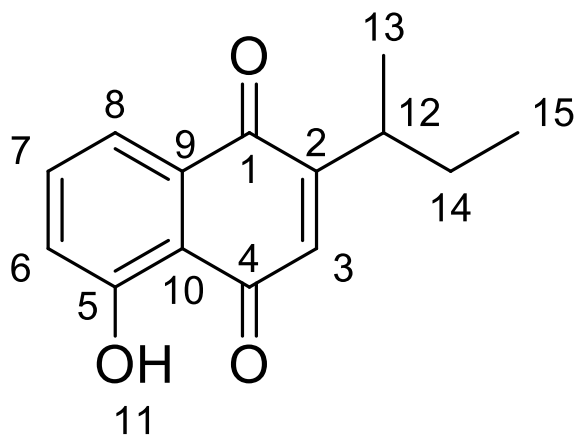
- Radical reaction
- Formation of regioisomers



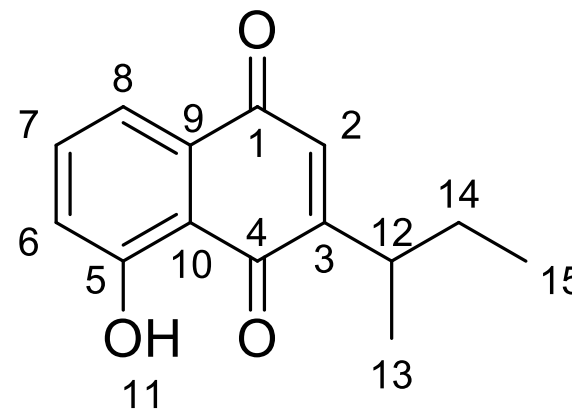
How to determine the chemical structure of each isolated regioisomers?

Structural elucidation

HMBC (Heteronuclear Multiple Bond Correlation) with NMR spectroscopy has been used to distinguish regioisomers.



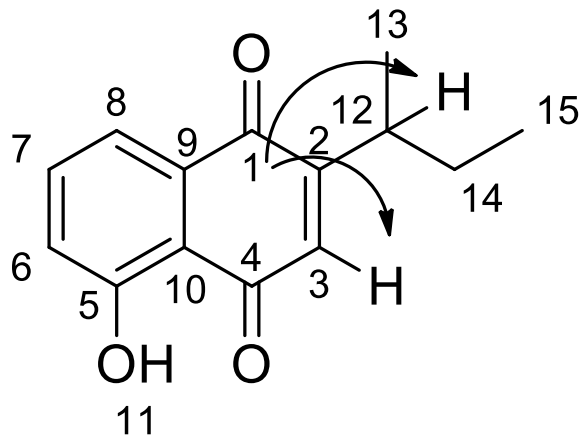
A



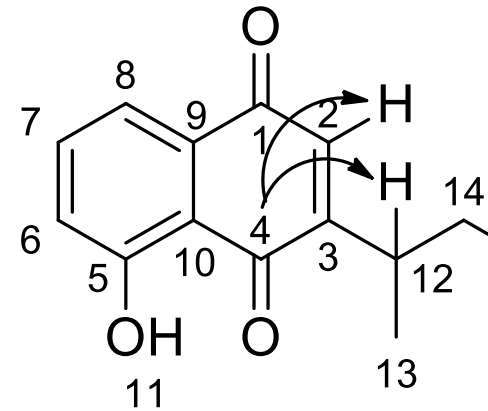
B

Structural elucidation

HMBC (Heteronuclear Multiple Bond Correlation) with NMR spectroscopy has been used to distinguish regioisomers.



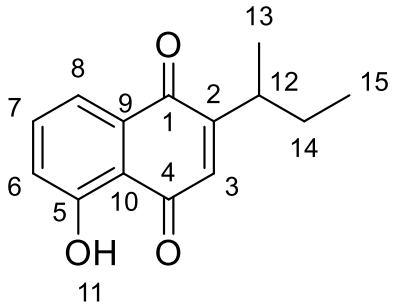
A



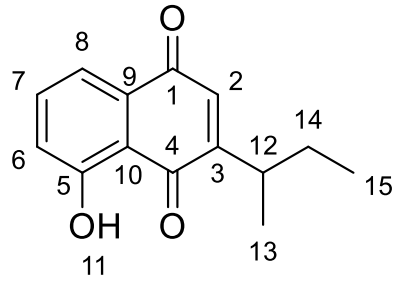
B

Structural elucidation

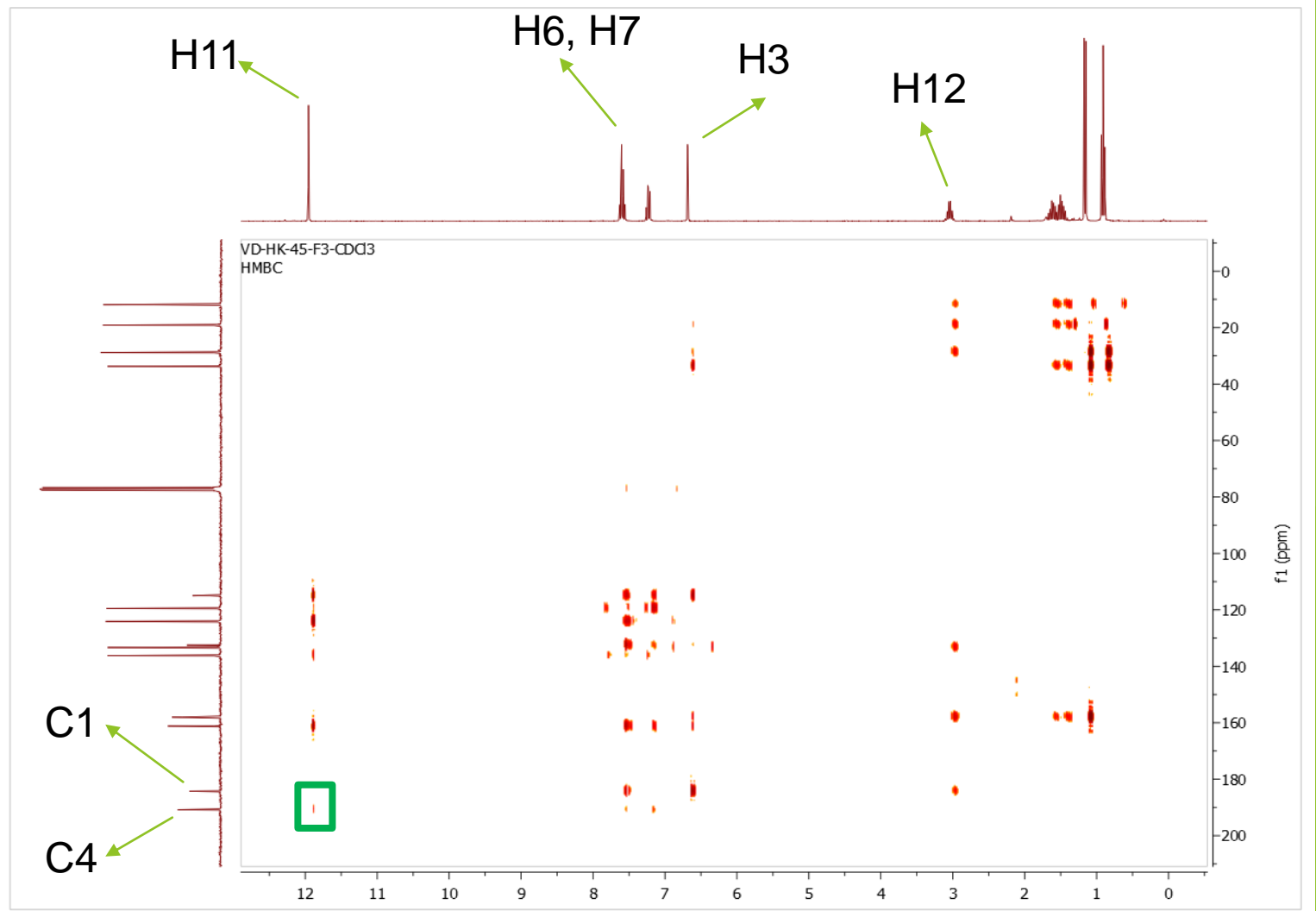
HMBC (Heteronuclear Multiple Bond Correlation).



A

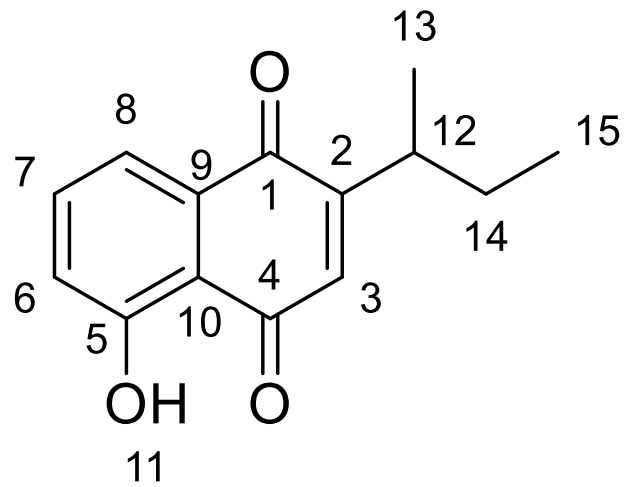


B

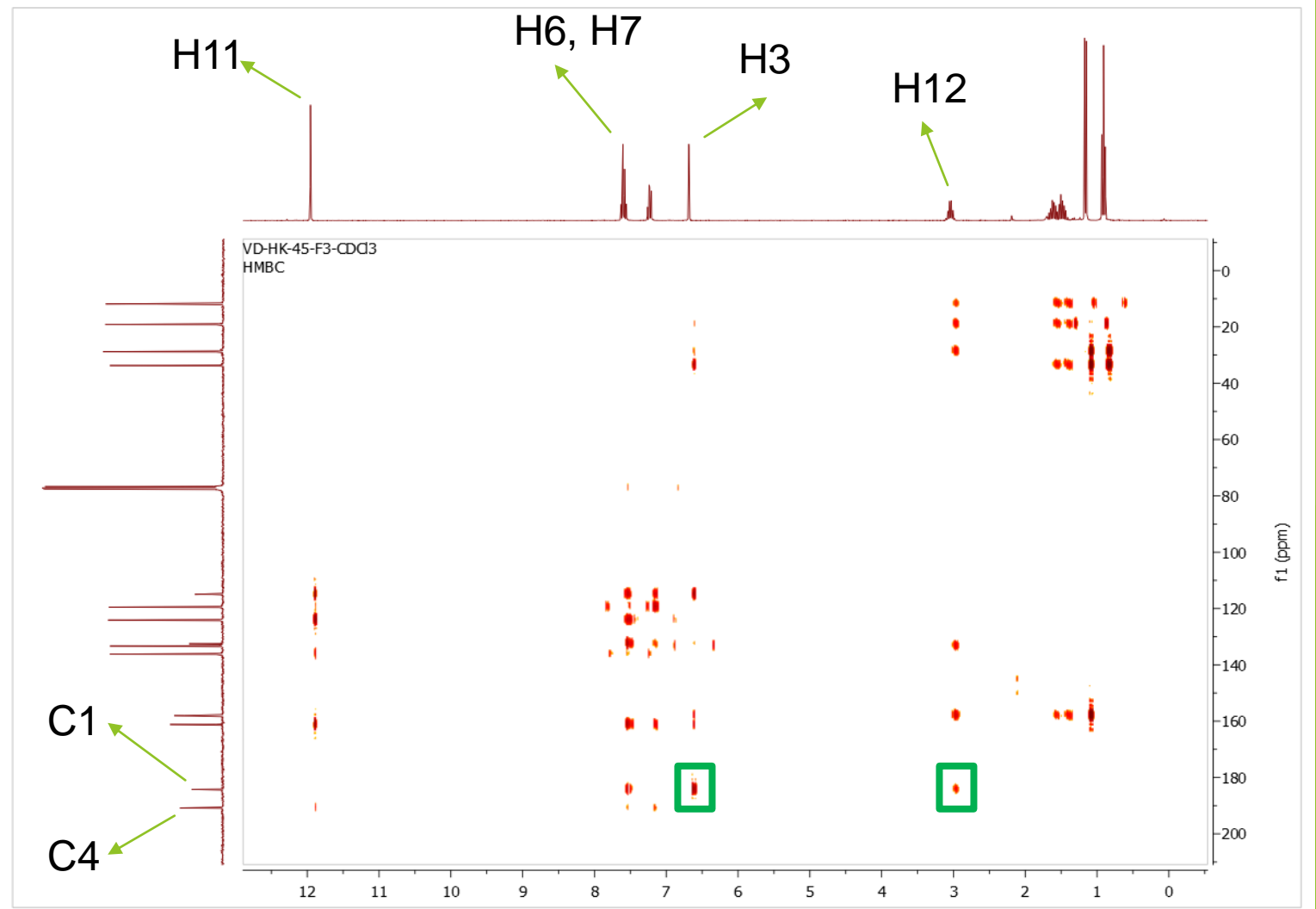


Structural elucidation

HMBC (Heteronuclear Multiple Bond Correlation).

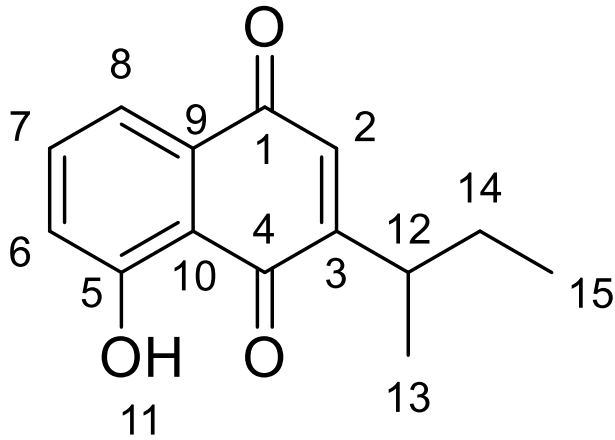


A

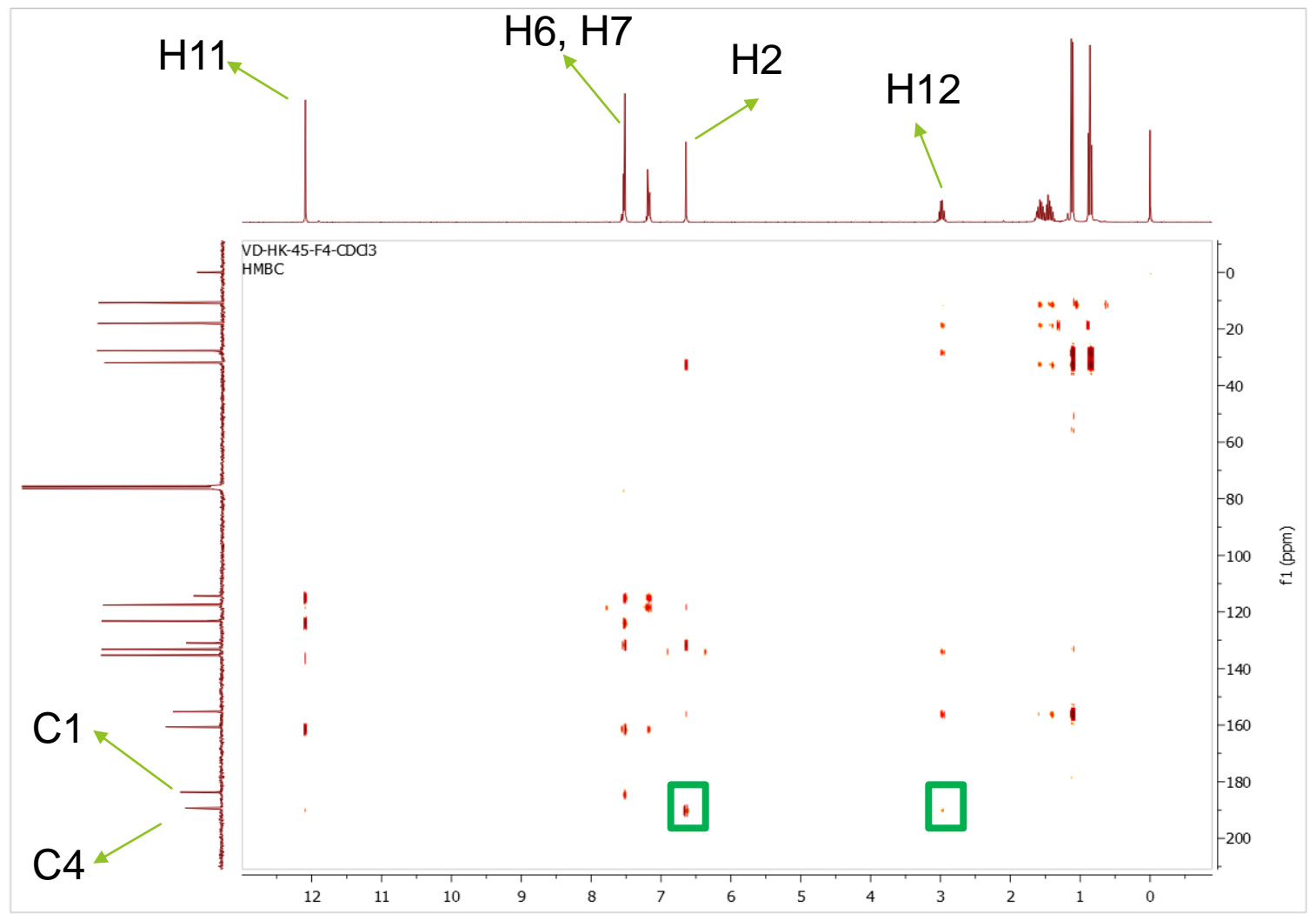


Structural elucidation

HMBC (Heteronuclear Multiple Bond Correlation).

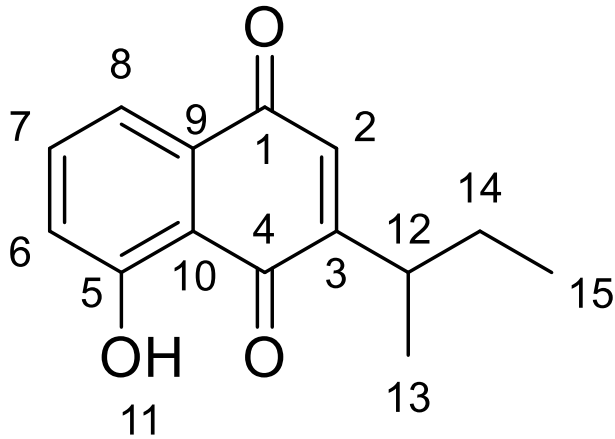


B



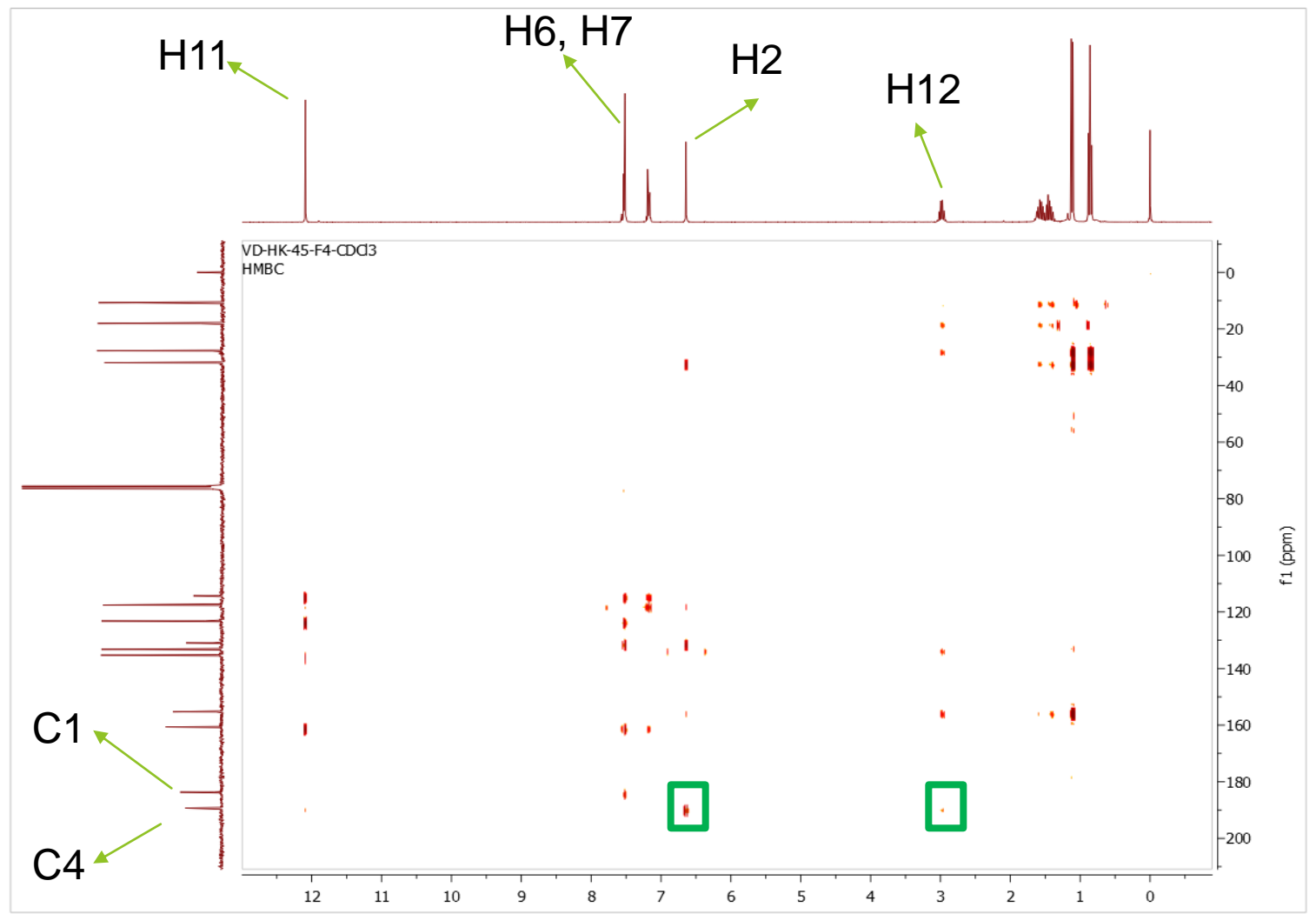
Structural elucidation

HMBC (Heteronuclear Multiple Bond Correlation).



B

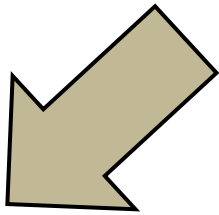
First structural elucidation on these derivatives



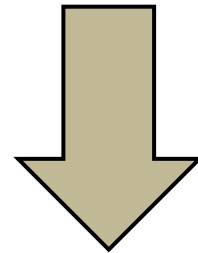
III. Conclusion & Perspectives

Conclusion & Perspectives

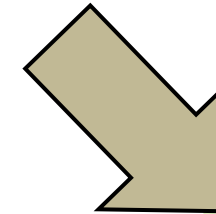
- ❖ 53 molecules were synthesized using this synthesis methodology
- ❖ Biologicals evaluations will allow the determination of the nature of the potential inhibition



Two component-systems disruptor ?
(as menadione)

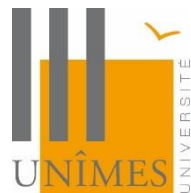


Efflux pumps inhibitor ?
(as menadione)



Bacteria wall disturber ?
(as menadione)

Dr. Cadière (MCF)
Pr. Mussard (PU)



Dr. H. Szurmant
(Ass. Prof.)



Western
University
OF HEALTH SCIENCES

Pr. Meffre (PU)
Dr. Benfodda (MCF)
David Bénimèlis (assistant engineer)



Pr. Lavigne (PUPH)
Dr. Dunyach-Rémy (PH)





Thank you for your attention

Waiting for your questions !

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21st September 2020

