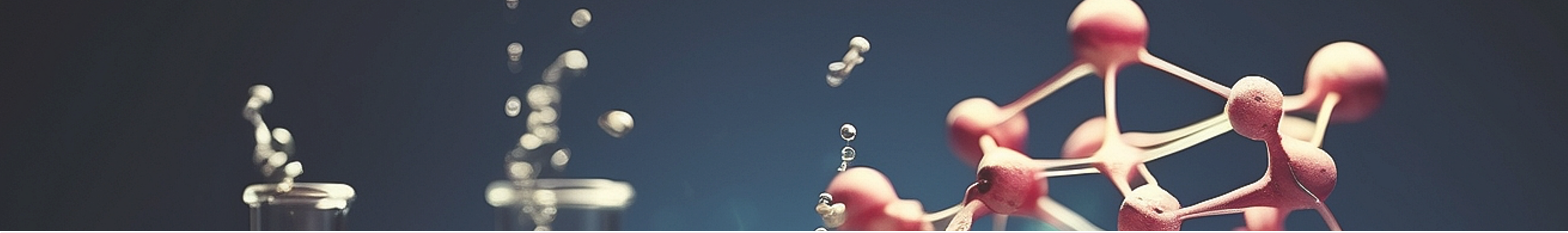

Six-membered phosphorus heterocycles

as versatile tools for bio-applications and material science

WORKSHOP INVESTIGACIÓN FACULTAD DE FARMACIA 2023

Anna Wolfram I C. Romero-Nieto Research Group (UCLM)

Can we still make major advances in chemistry?

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Can we still make major advances in chemistry?

YES WE CAN!

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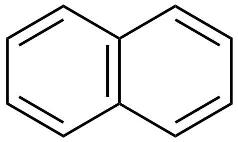

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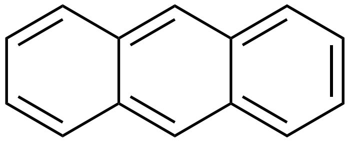
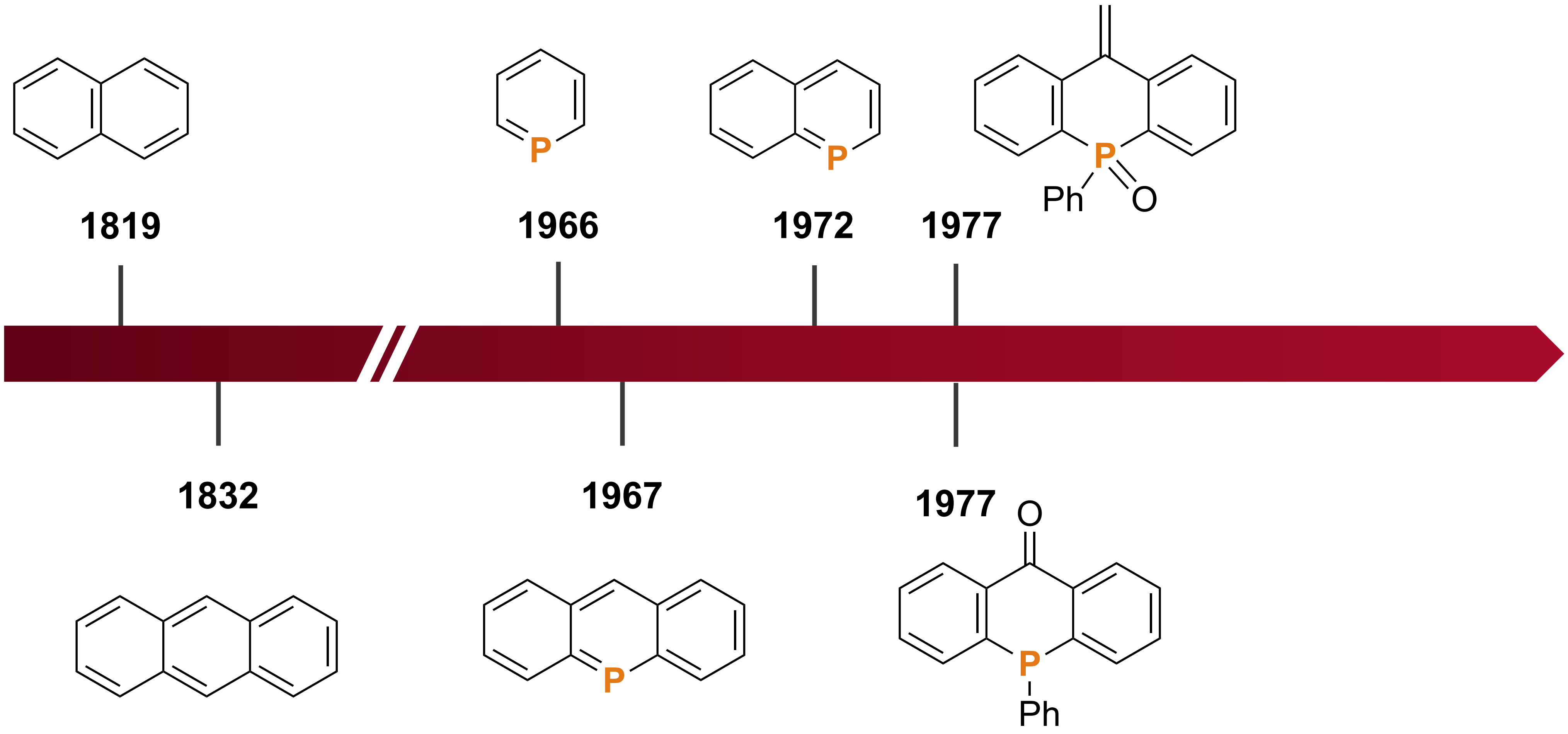
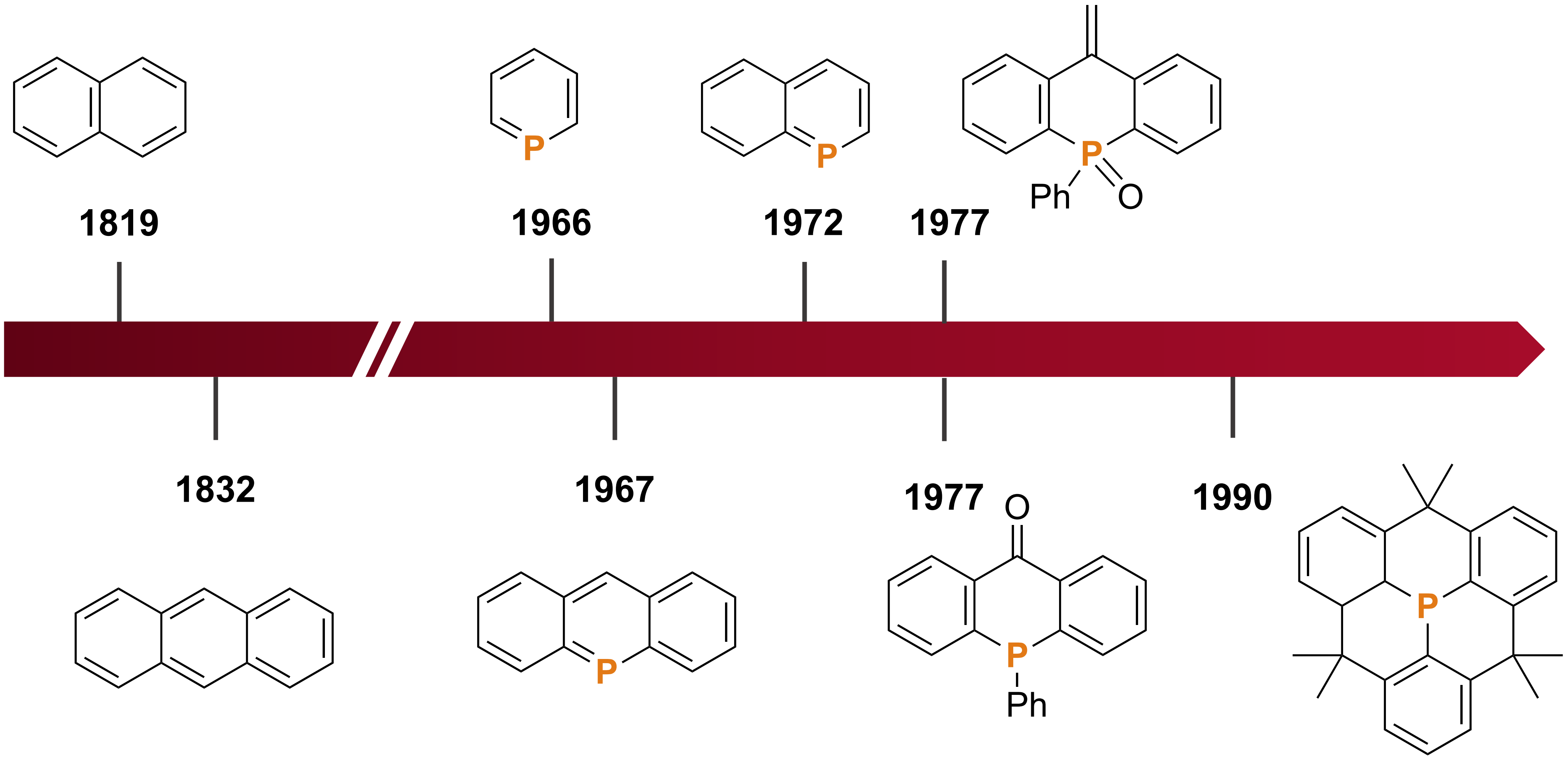


Regulska, E., Romero-Nieto C. *Dalton Trans.* **2018**, *47*, 10344



Regulska, E., Romero-Nieto C. *Dalton Trans.* **2018**, *47*, 10344

Advancing scientific frontiers: Innovations in phosphorus heterocycles



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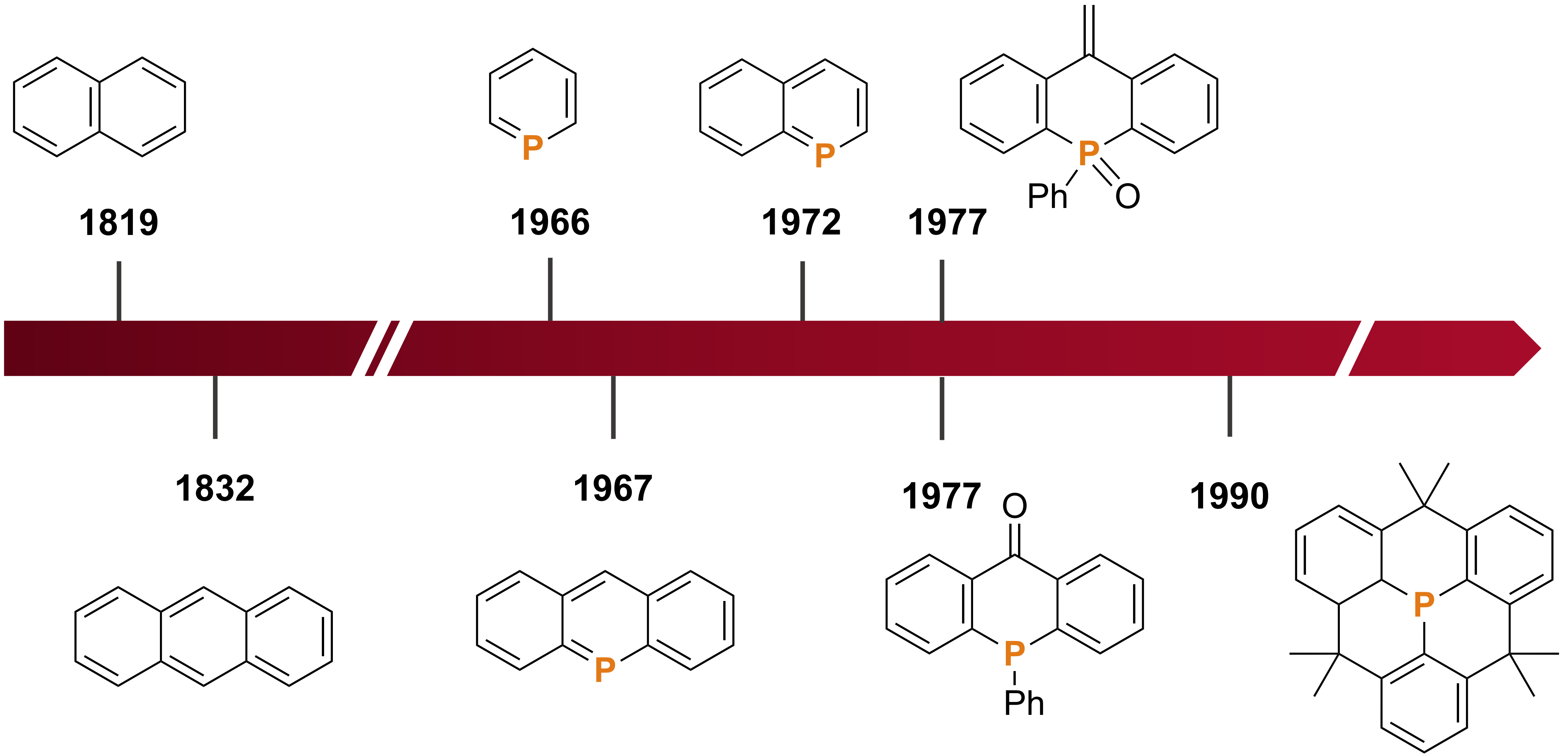

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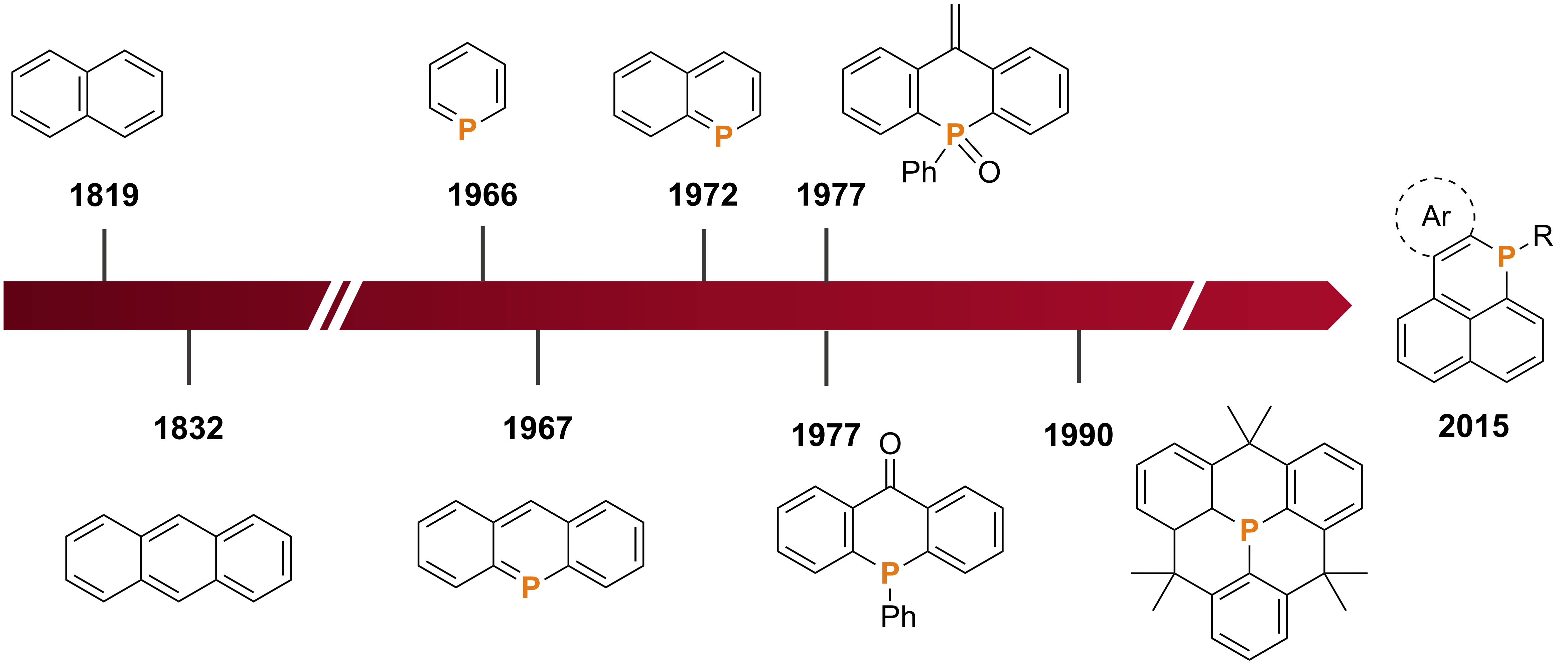

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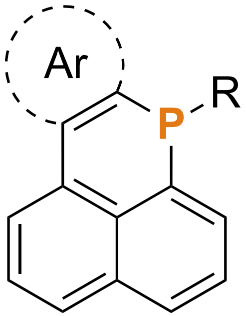

2015

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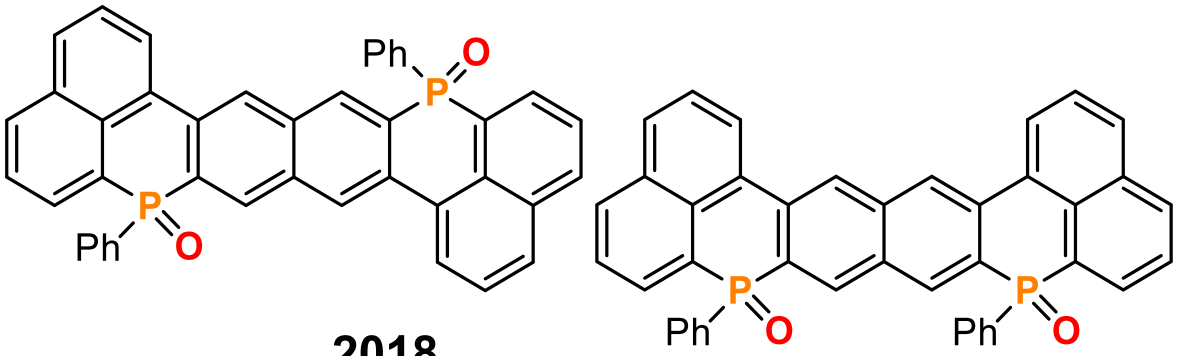
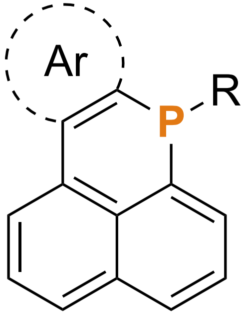
Phosphaphenalene



2018

Romero-Nieto, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 15157.

Diphosphahexaarenes



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Phosphaphenalene

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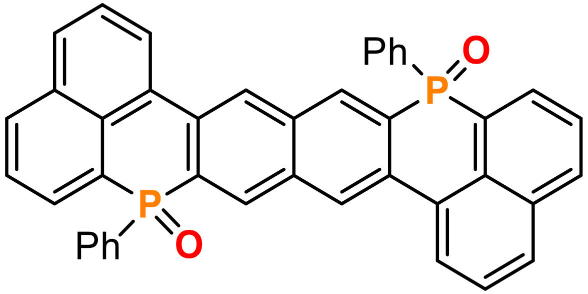

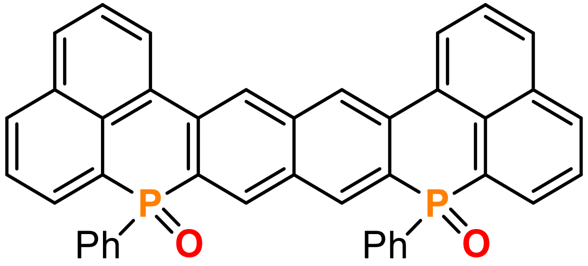

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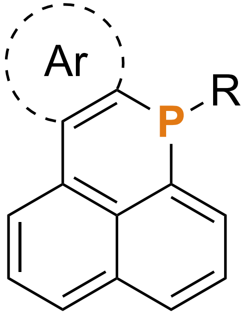

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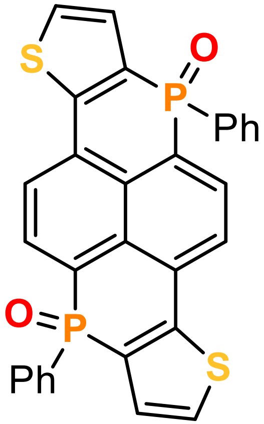
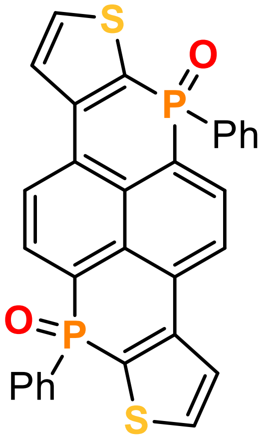
Phosphaphenalene

Diphosphapyrenes

2021





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Pushing scientific frontiers: Renaissance of 6-membered P-heterocycles

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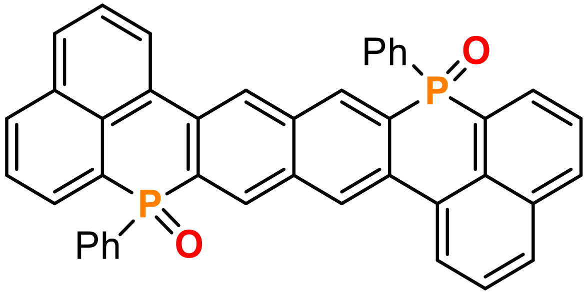

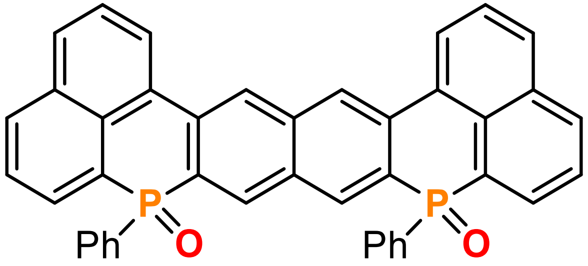

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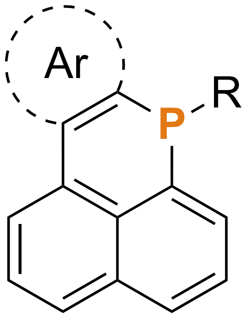

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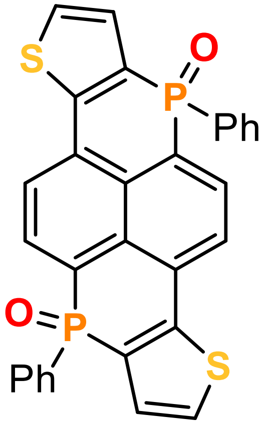
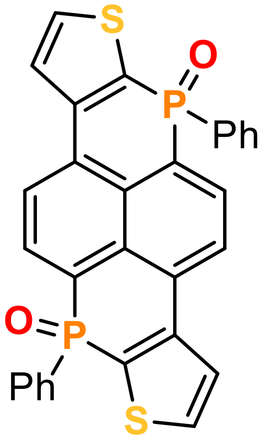
Phosphaphenalene

Diphosphapyrenes

2021





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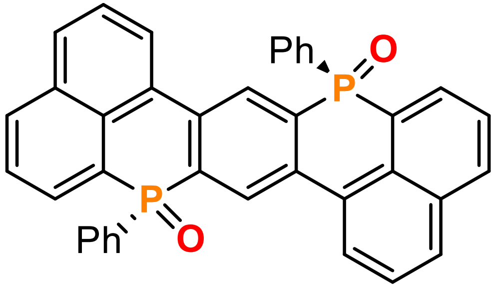
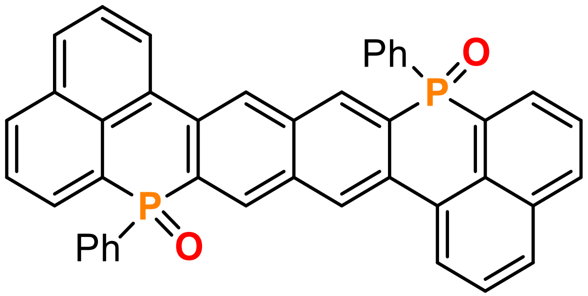
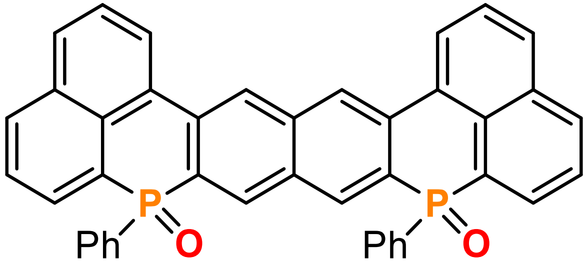


Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19

Diphosphapentaarenes

Pushing scientific frontiers: Renaissance of 6-membered P-heterocycles





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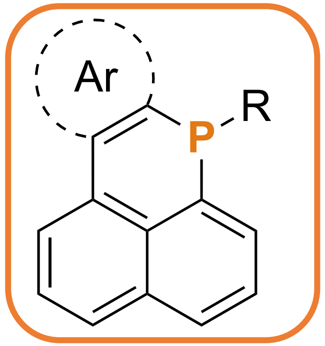
2018

Diphosphahexaarenes



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Phosphaphenalene

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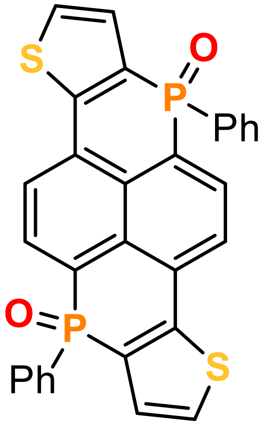
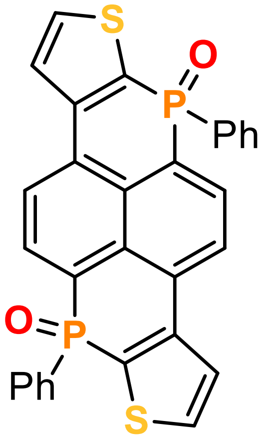
2021





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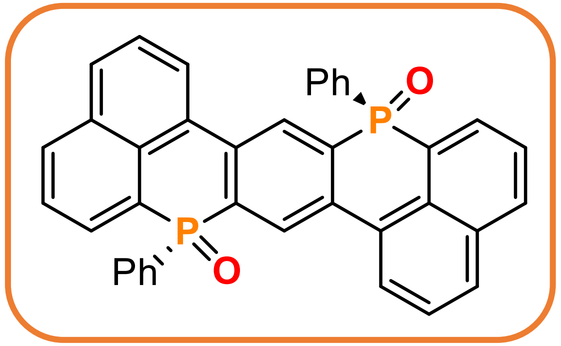

Regulska, E. *Chem. Eur. J.* **2022**.
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Diphosphapentaarenes

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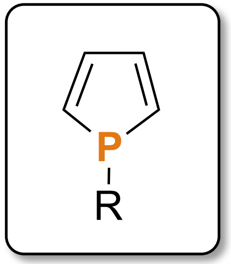
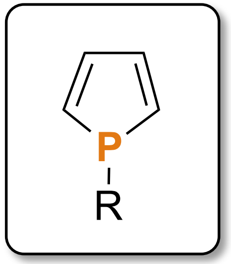
Phosphole



- **Variety of P-functionalisations**
- **Modulation of electronic properties**

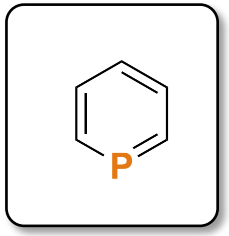
Forging pathways to a novel molecular system

Phosphole



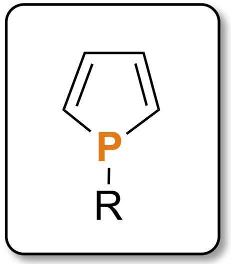
- Variety of P-functionalisations
- Modulation of electronic properties

Phosphinine



- High electron delocalisation
- σ-donor/π-acceptor character

Phosphole



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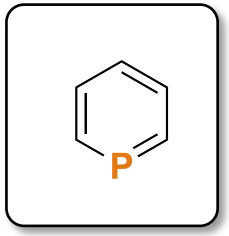

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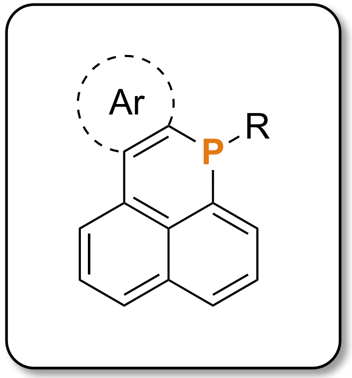


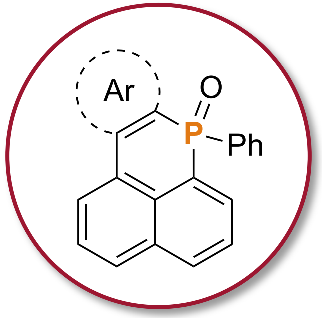
Phosphaphenalene

- High electron delocalization
- Easily accessible phosphorus centre
- Air stability
- Versatile P-postfunctionalisations

One system for generating a diverse array of molecules

Philip Hindenberg

Carlos Romero-Nieto



Romero-Nieto, C., Hindenberg, P. *Synlett,* **2016,** *27*, 2293–2300.

One system for generating a diverse array of molecules

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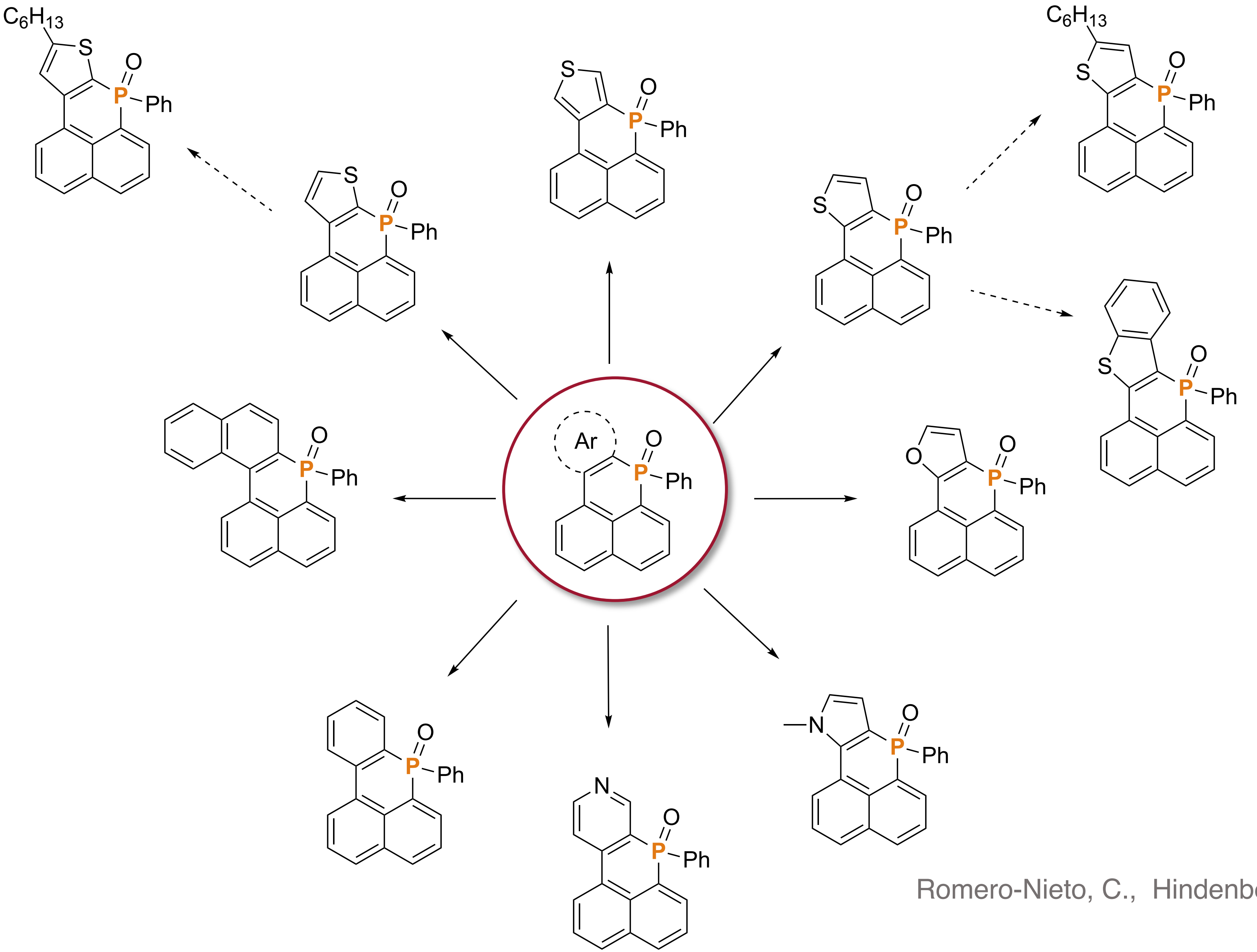


Philip Hindenberg


Carlos Romero-Nieto

Romero-Nieto, C., Hindenberg, P. *Synlett,* **2016,** *27*, 2293–2300.

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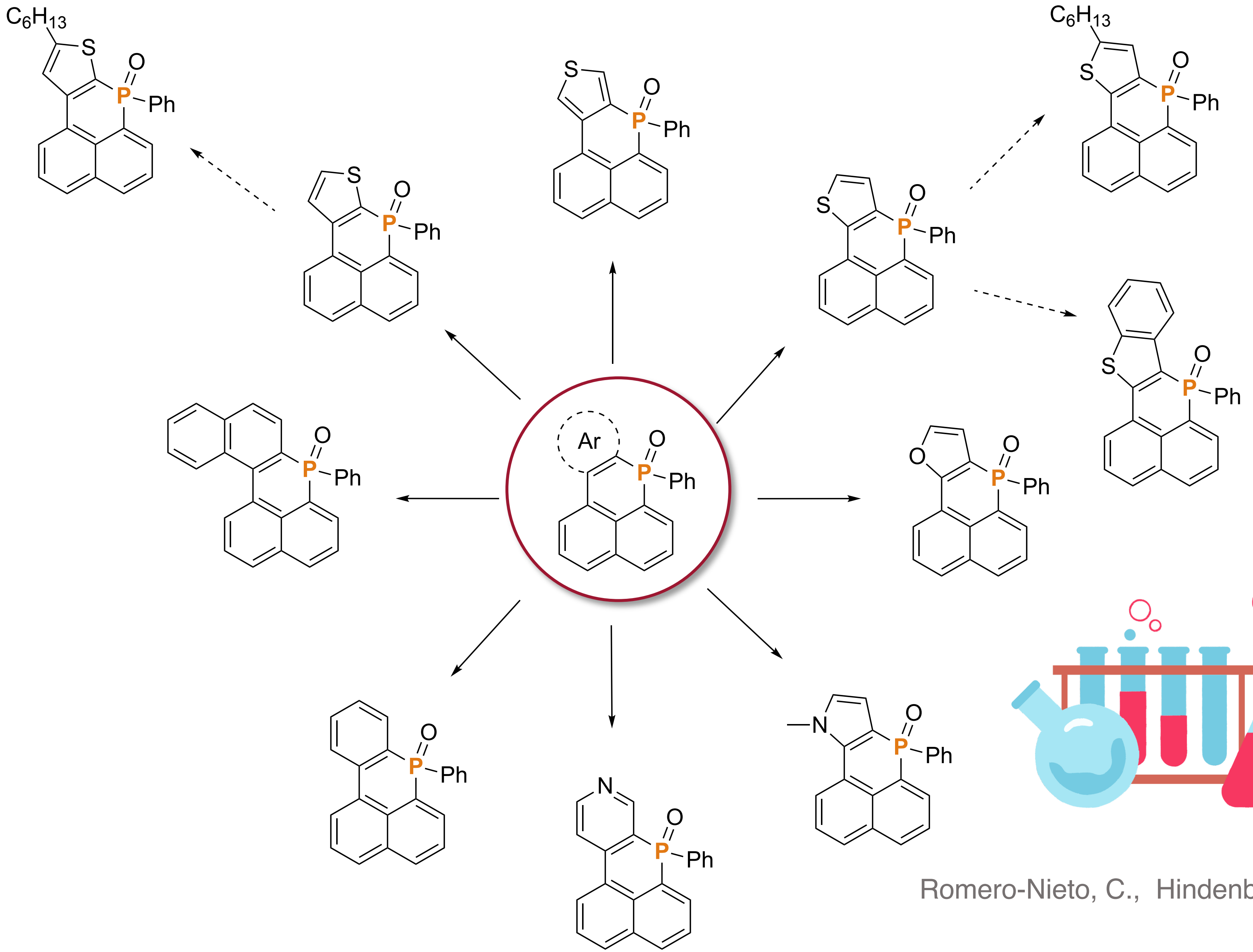
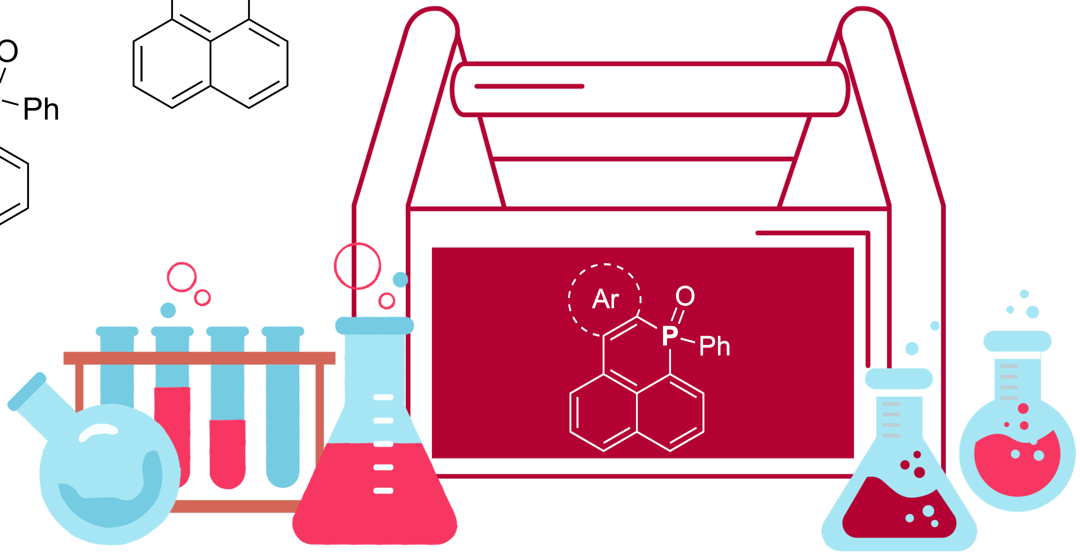


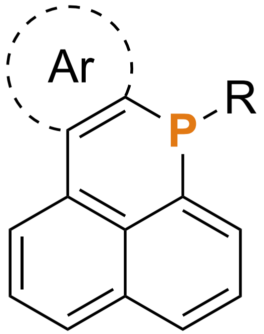
Philip Hindenberg

Carlos Romero-Nieto

Molecular toolbox



Romero-Nieto, C., Hindenberg, P. *Synlett,* **2016,** *27*, 2293–2300.



Phosphaphenalene

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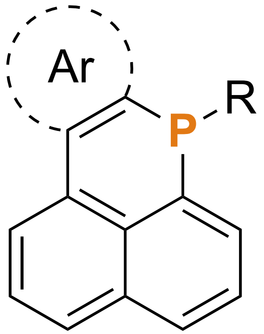

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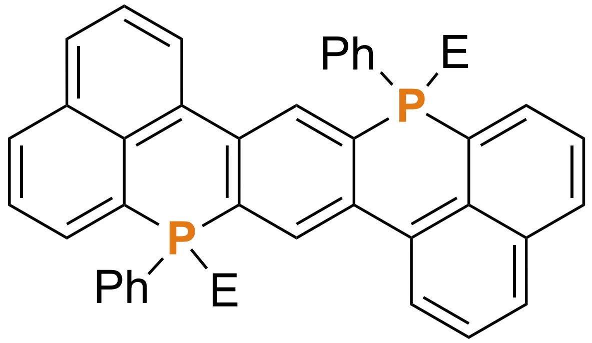
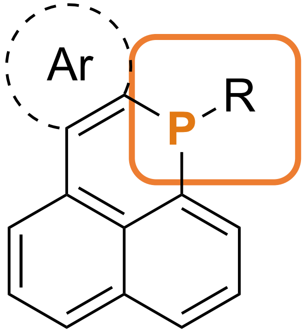


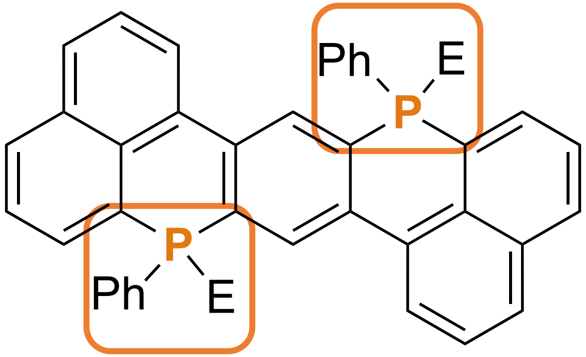
E = O, S, Me

Diphosphapentaarenes

UCLM



Accessible P-centre



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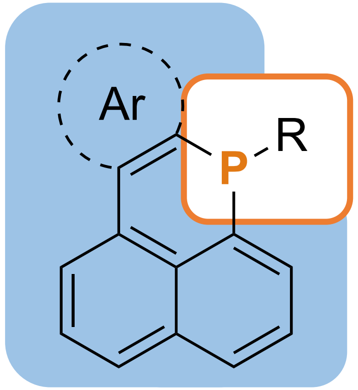
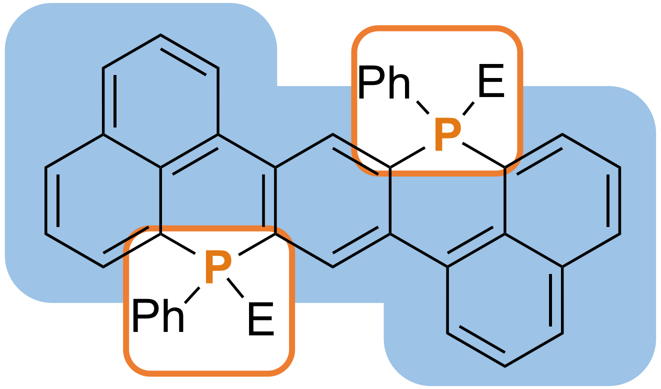
Phosphaphenalene

Diphosphapentaarenes



Accessible P-centre

Tuneable backbone



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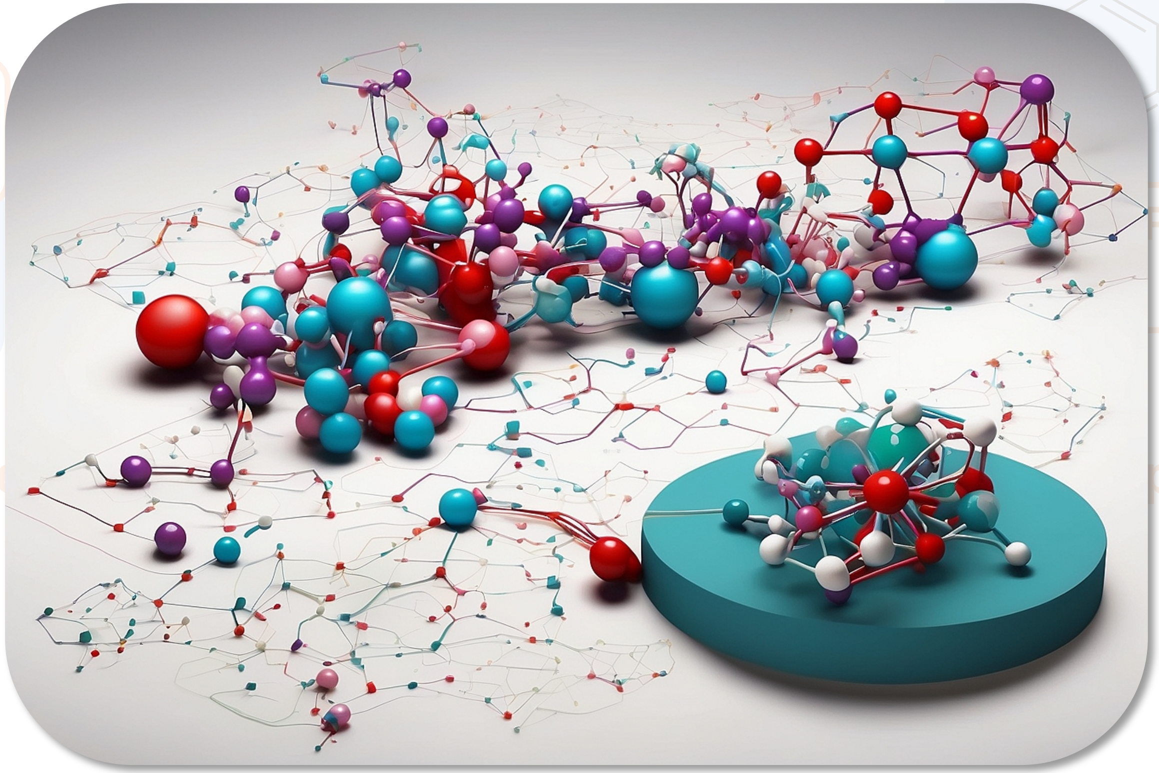
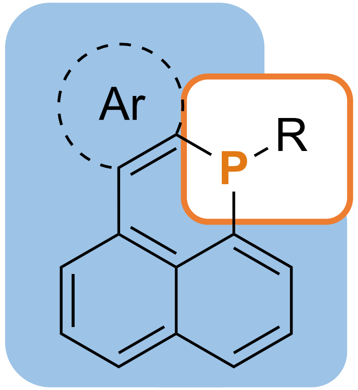
Phosphaphenalene

Diphosphapentaarenes



Molecular platforms for rational design

UCLM



Phosphaphenalene

Accessible P-centre

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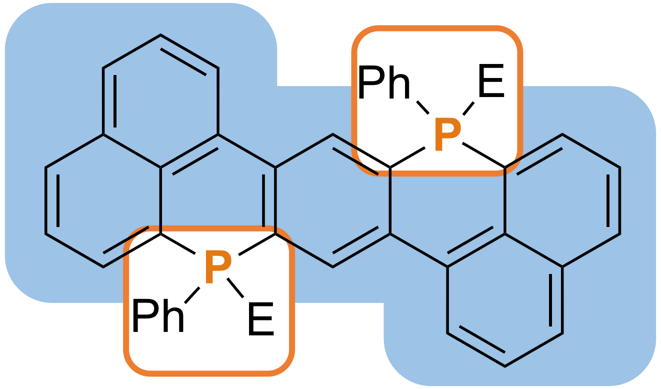


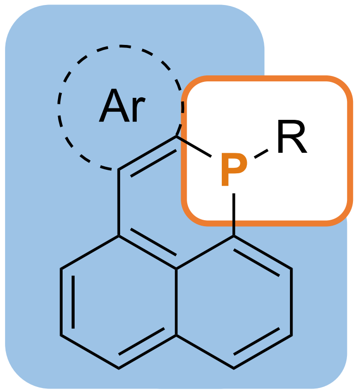
E = O, S, Me

Diphosphapentaarenes

Application case I

Rational drug optimisation based on structure-activity relationship

UCLM



Accessible P-centre

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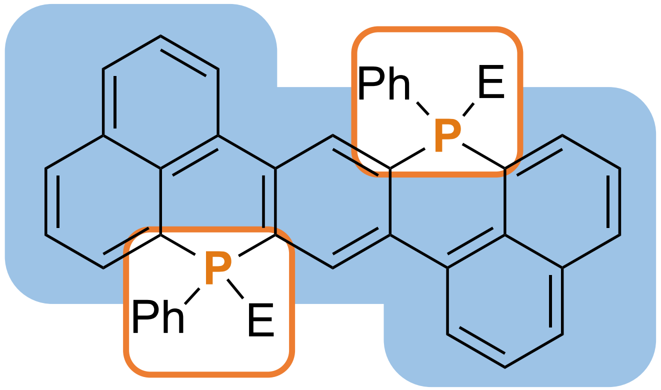


E = O, S, Me

Phosphaphenalene

Diphosphapentaarenes

Application case I

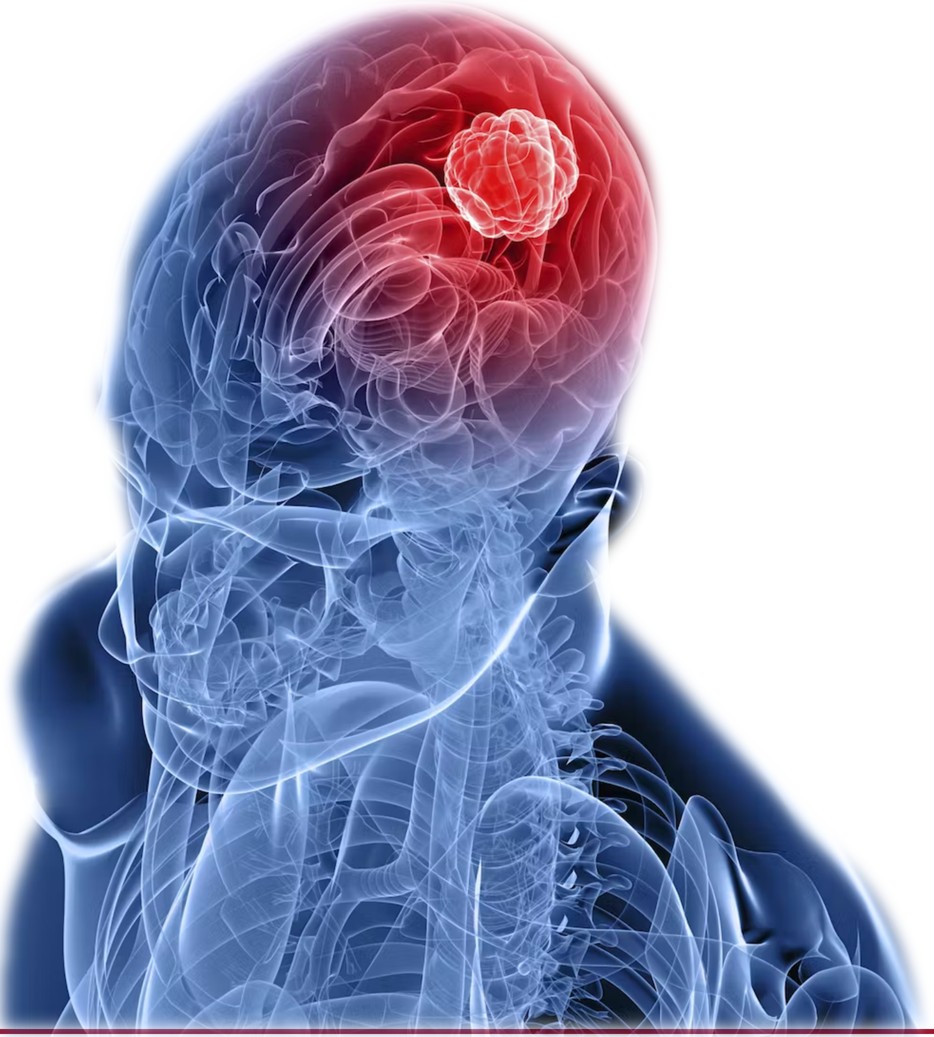
Rational drug optimisation based on structure-activity relationship

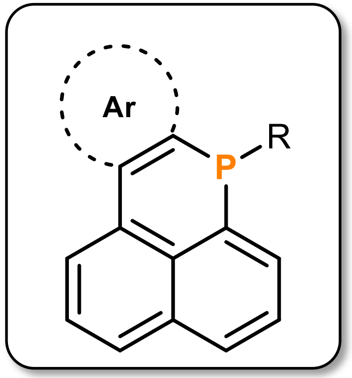
Application case II

Finetuning optoelectronic properties for advanced organic materials

UCLM

Glioblastoma (GBM)

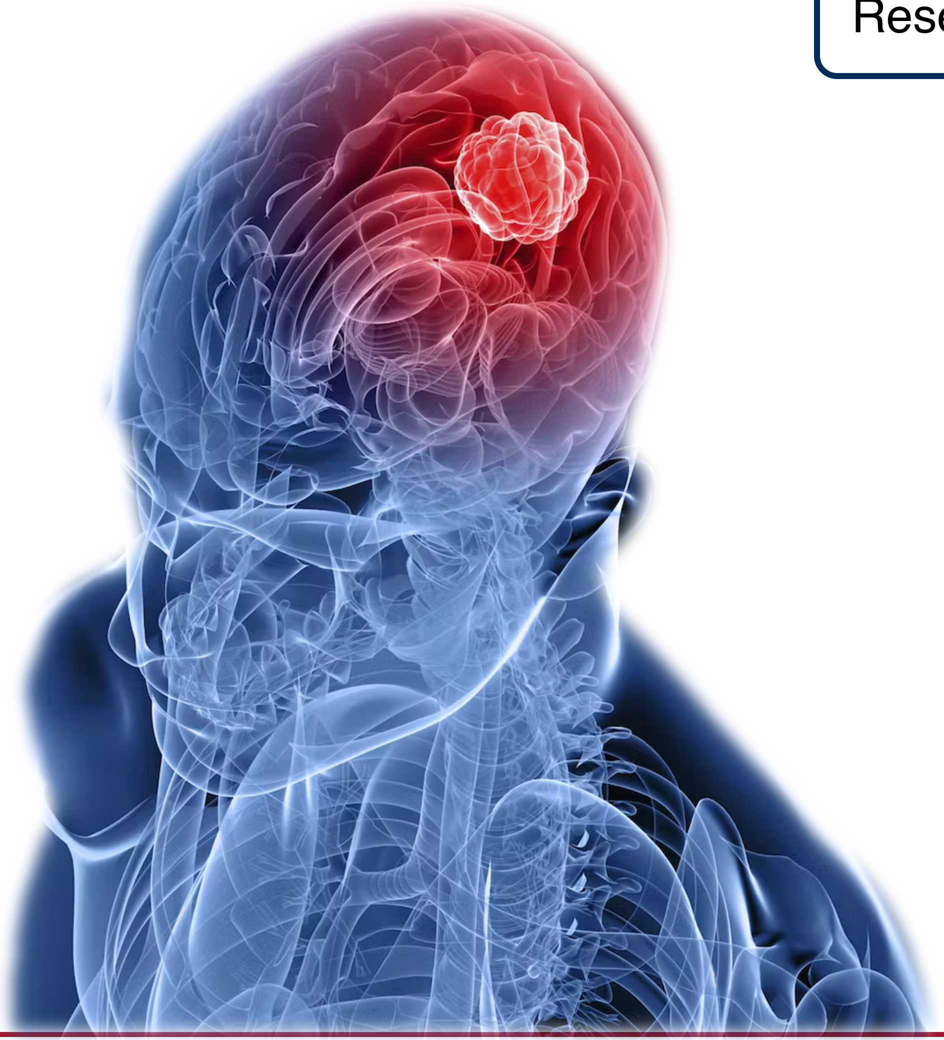




Phosphaphenalene

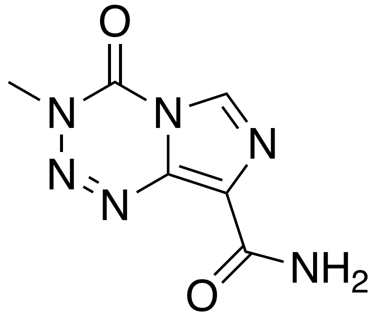
UCLM

Glioblastoma (GBM)



Current treatment (Stupp protocol, 2005)

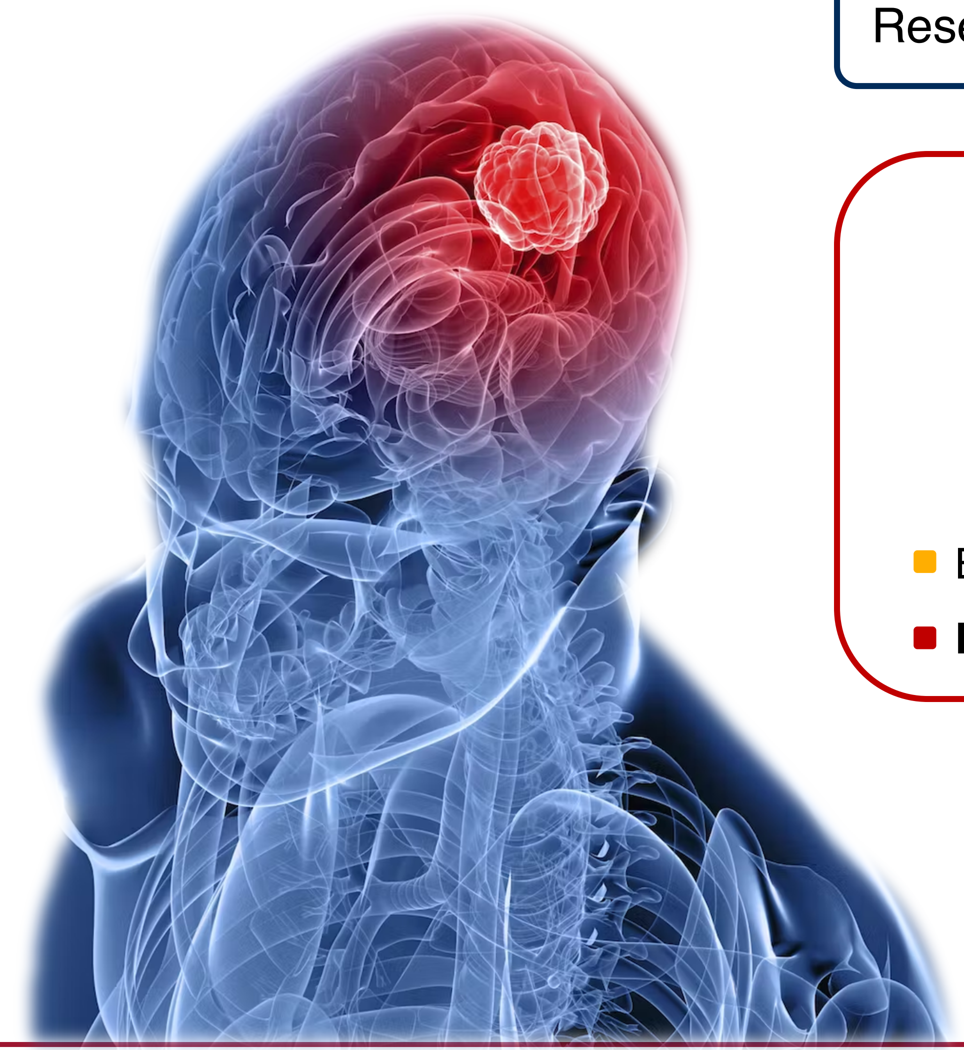
Resection	Radio-therapy	Chemotherapy with **alkylating agents**



TMZ
Temozolomide

Application I: Unlocking the potential of phosphaphenalenes for bio-applications

Glioblastoma (GBM)



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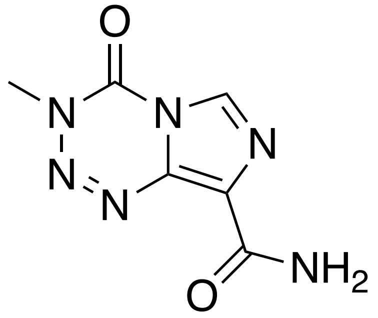
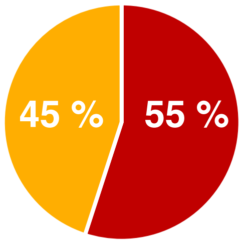


TMZ
Temozolomide

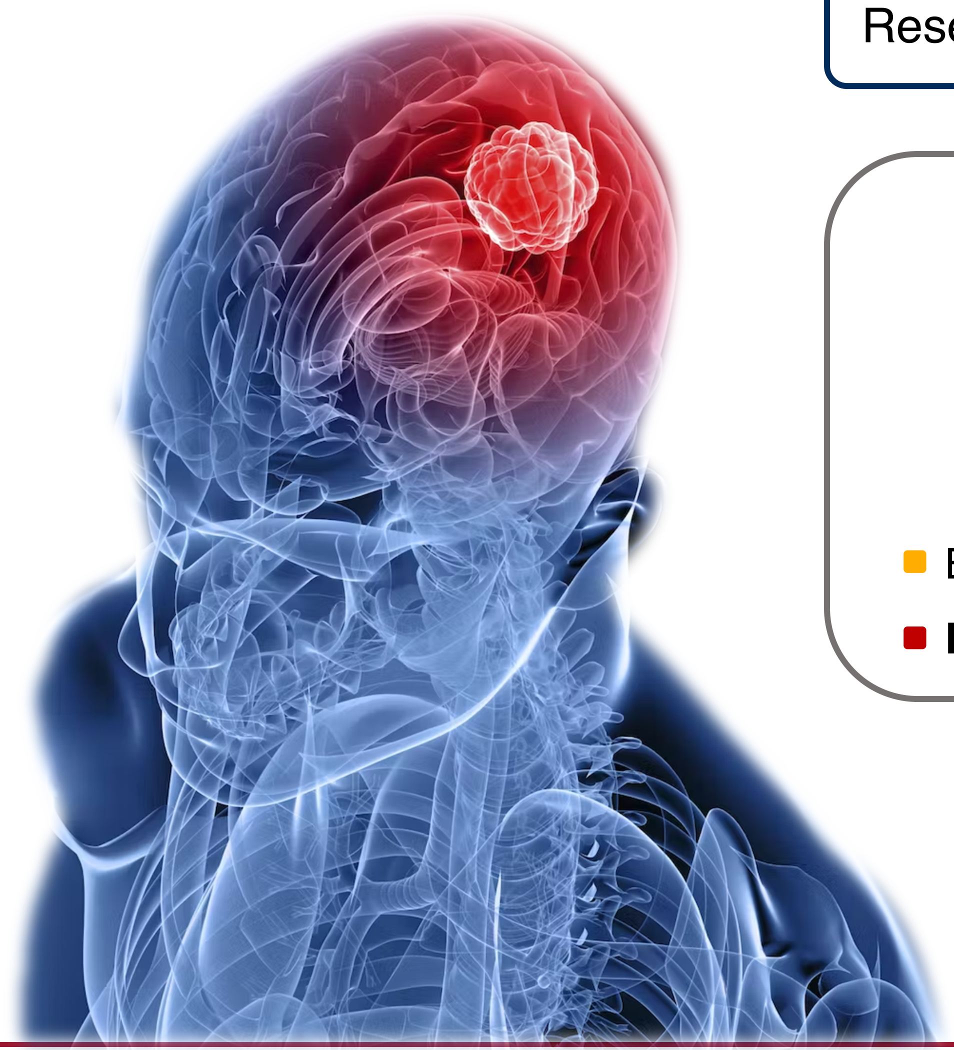
Patient's response



- Benefit from TMZ
- **Do not benefit from TMZ**

Application I: Unlocking the potential of phosphaphenalenes for bio-applications

Glioblastoma (GBM)



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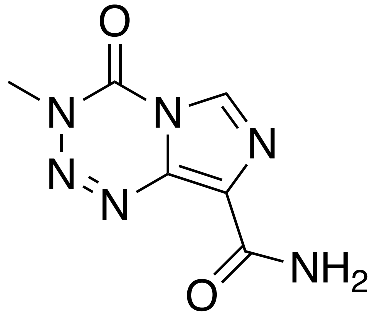

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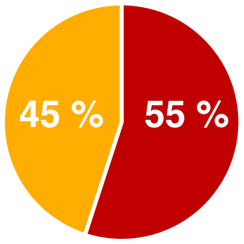

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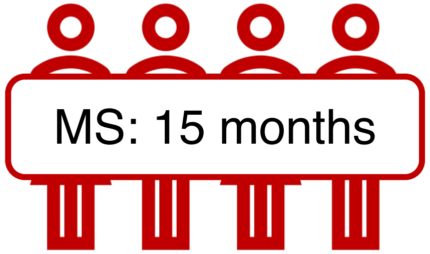
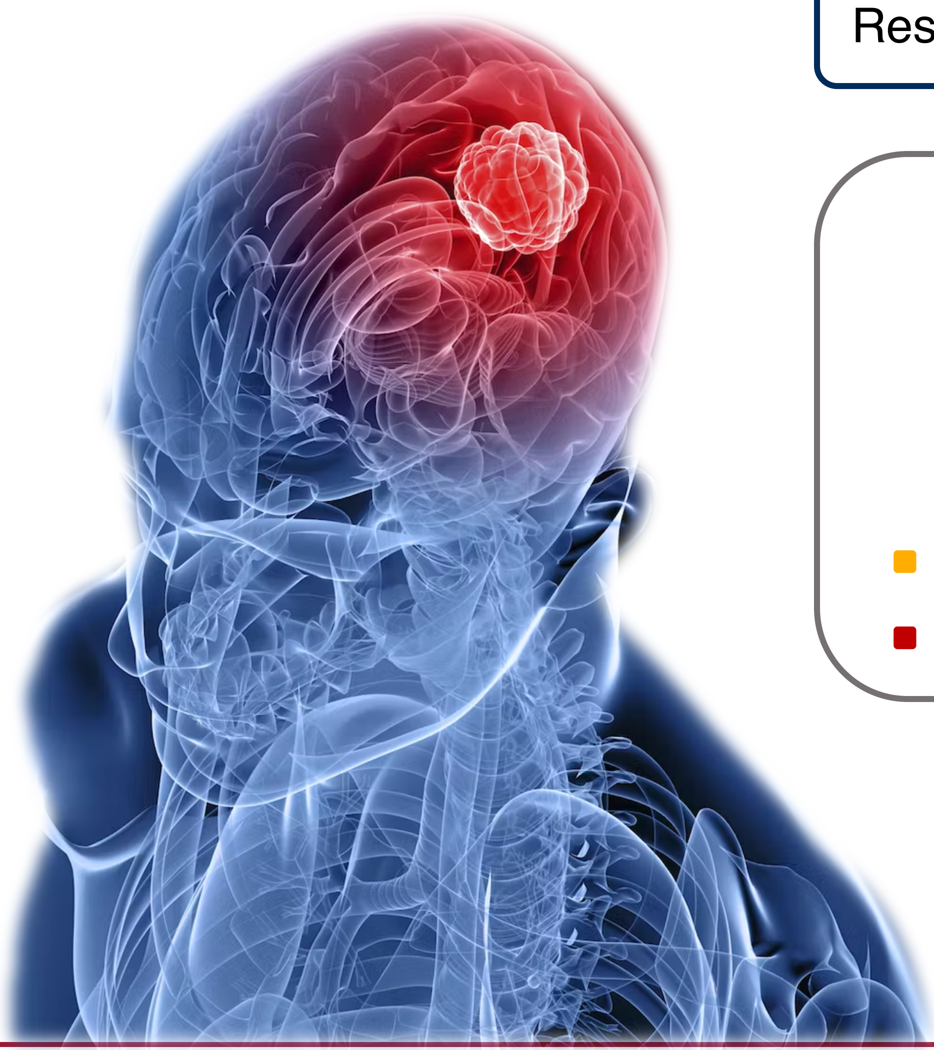


Application I: Unlocking the potential of phosphaphenalenes for bio-applications

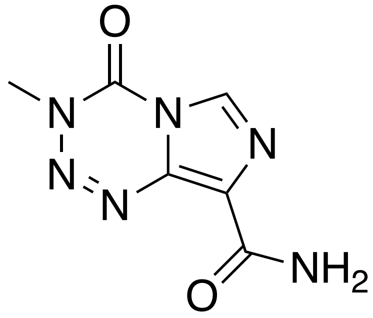
UCLM

Glioblastoma (GBM)



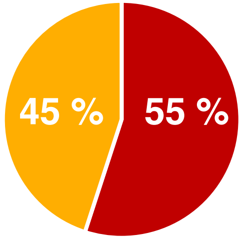
Current treatment (Stupp protocol, 2005)

Resection	Radio-therapy	Chemotherapy with **alkylating agents**

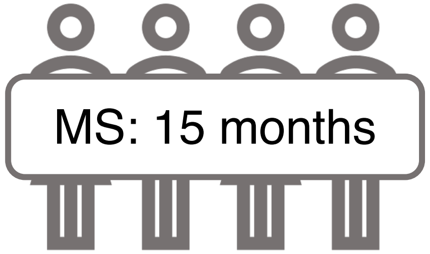


TMZ
Temozolomide

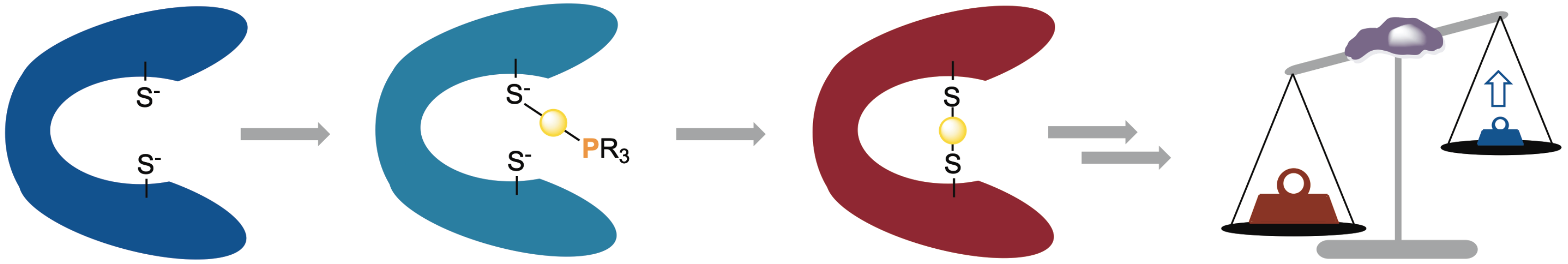
Patient's response



- Benefit from TMZ
- **Do not benefit from TMZ**



! Urgent need for novel agents !



Active disulfide reductase

Redox-active thiol coordination

Inactive disulfide reductase

Decrease in redox homeostasis

Wolfram A. *Nanoscale*, **2022**, *14*, 17500.

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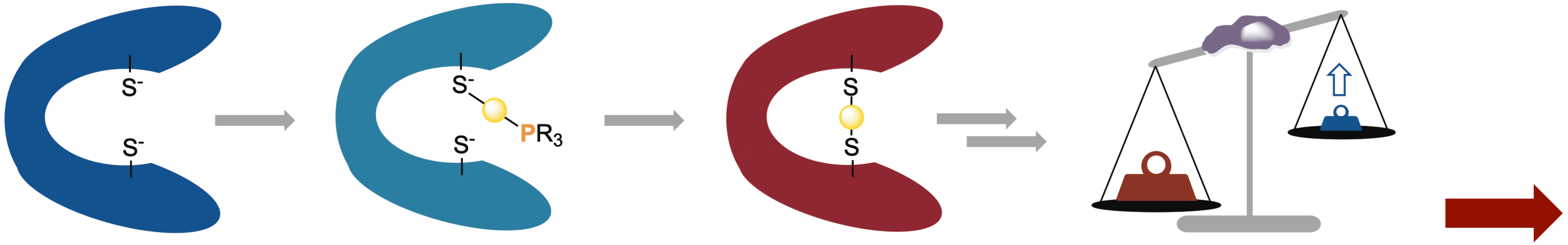
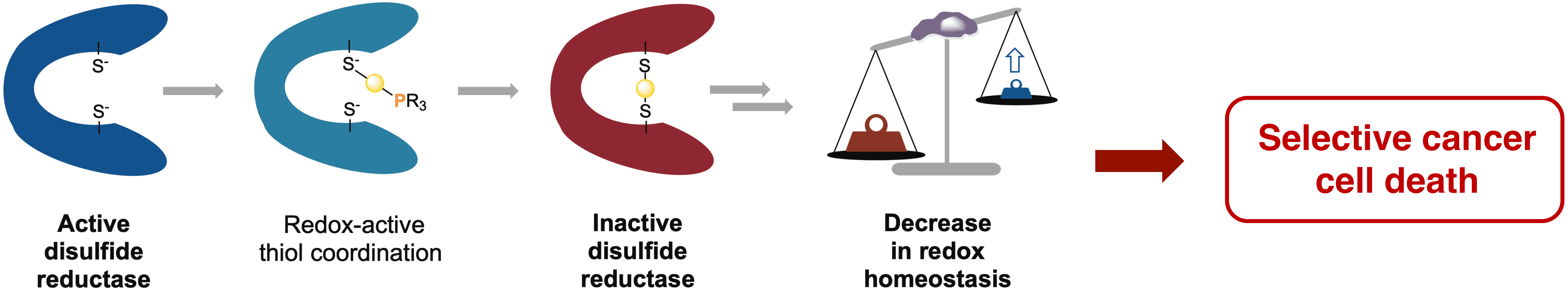


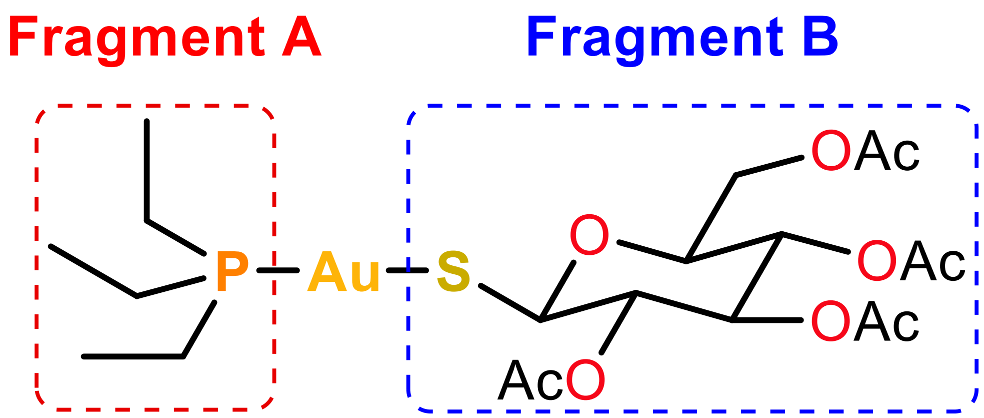
Active disulfide reductase | Redox-active thiol coordination | **Inactive disulfide reductase** | **Decrease in redox homeostasis**

Selective cancer cell death

Wolfram A. *Nanoscale*, **2022**, *14*, 17500.

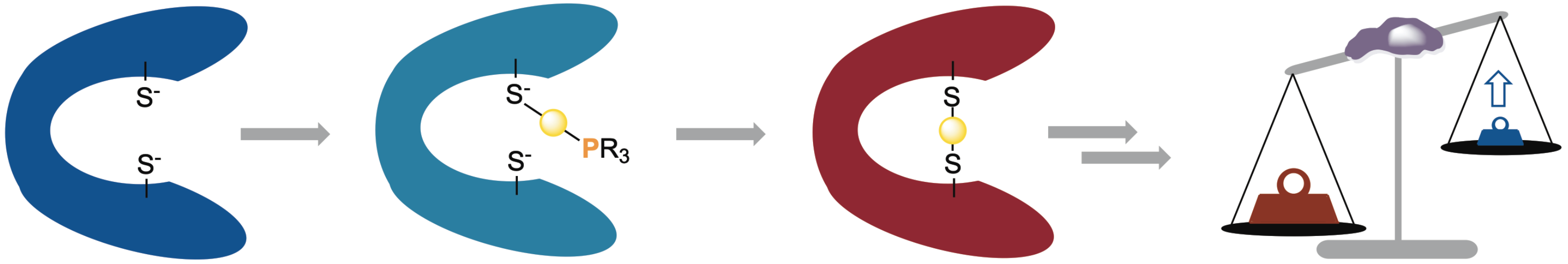


Gold(I) agents as potent *in vitro* agents



Wolfram A. *Nanoscale*, **2022**, *14*, 17500.

Application I: Unlocking the potential of phosphaphenalenes for bio-applications



Active disulfide reductase

Redox-active thiol coordination

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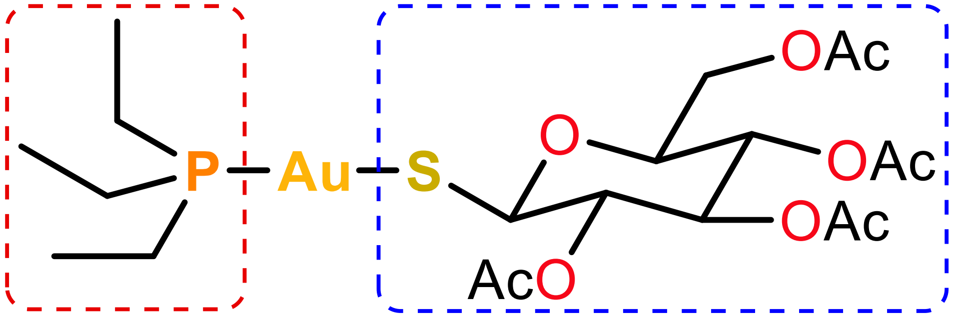
Selective cancer cell death

Gold(I) agents as potent *in vitro* agents

Fragment A

Fragment B



Linear agents lack *in vivo* efficacy due to poor stability, reduced solubility, and consequently, poor bioavailability.

Wolfram A. *Nanoscale*, **2022**, *14*, 17500.

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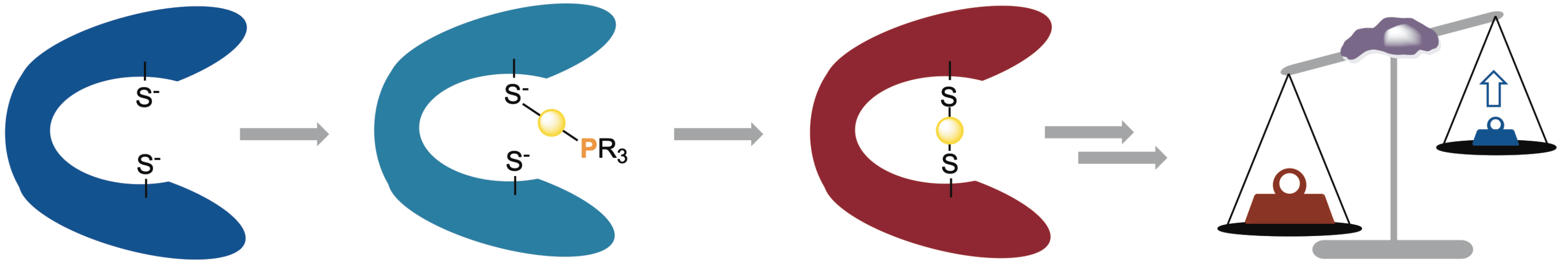
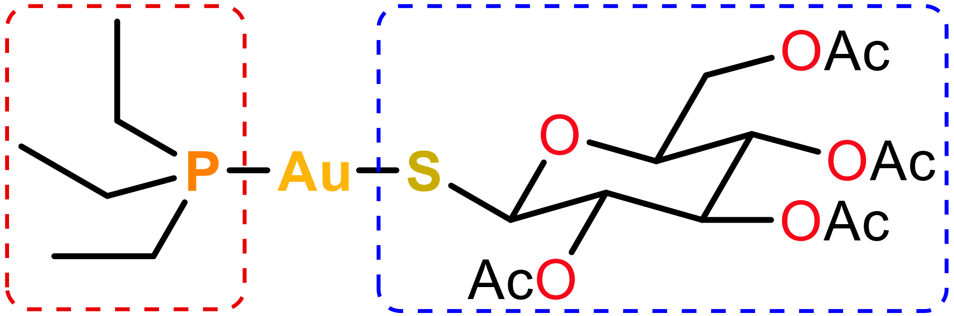


Active disulfide reductase	Redox-active thiol coordination	**Inactive disulfide reductase**	**Decrease in redox homeostasis**

Selective cancer cell death

Gold(I) agents as potent *in vitro* agents

Fragment A **Fragment B**

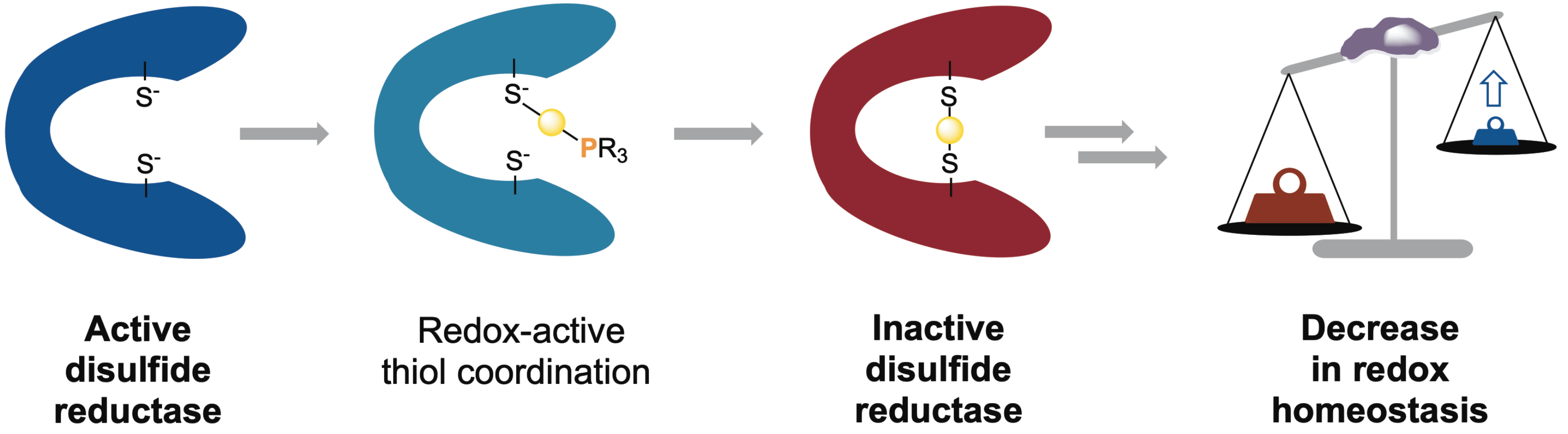


Linear agents lack *in vivo* efficacy due to poor stability, reduced solubility, and consequently, poor bioavailability.

Linear agents DO NOT offer facile tunability at fragment A.

Wolfram A. *Nanoscale*, **2022**, *14*, 17500.

Application I: Unlocking the potential of phosphaphenalenes for bio-applications



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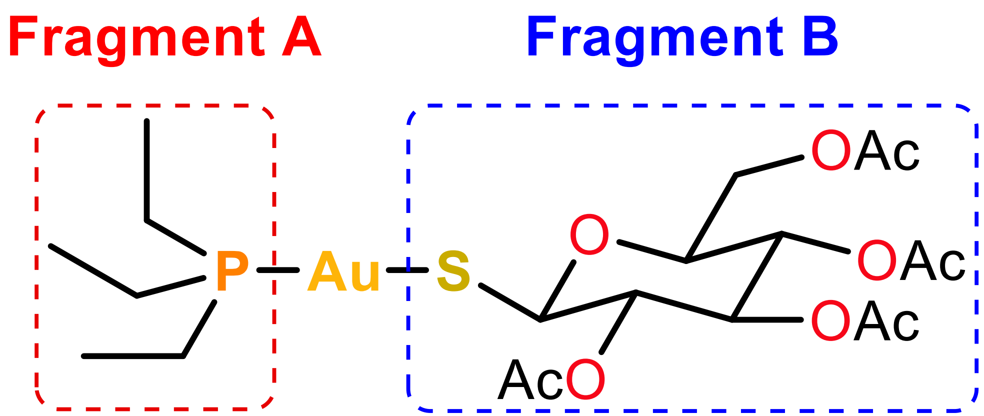
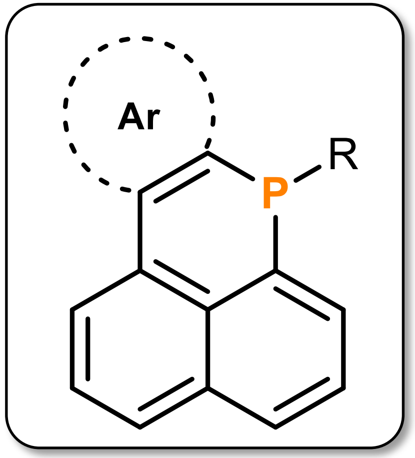
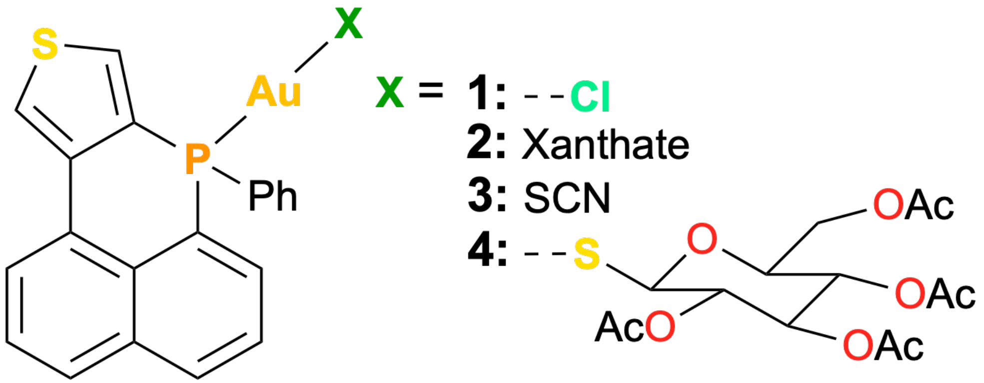




Phosphaphenalene agents DO!

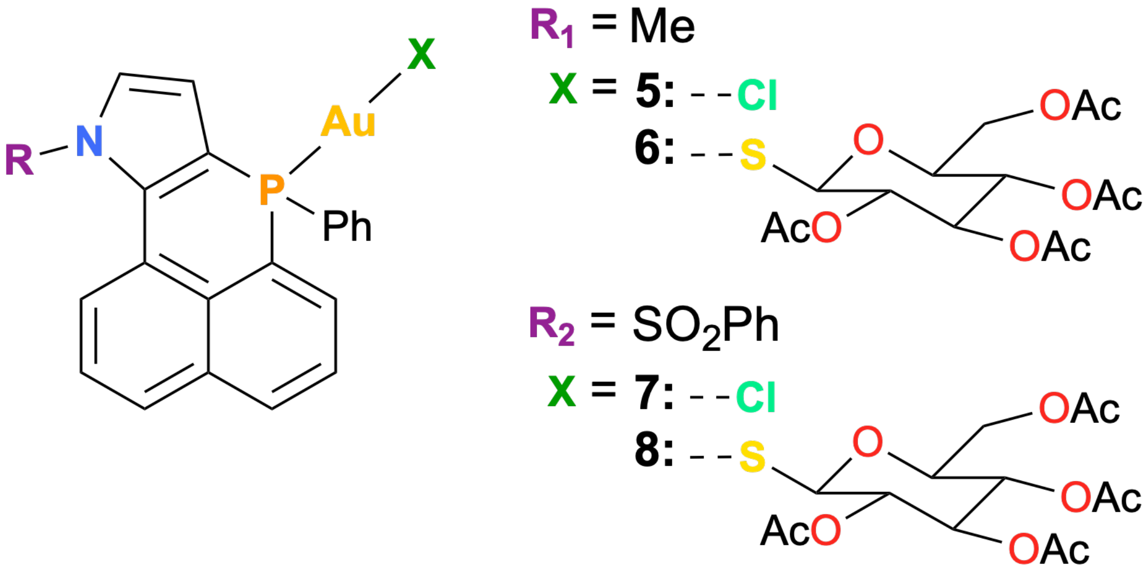
Wolfram A. *Nanoscale*, **2022**, *14*, 17500.

Application I: Unlocking the potential of phosphaphenalenes for bio-applications



1st generation

Roesch S., *Chem. Commun.* **2020**, *56*, 14593-14596.



2nd generation

Fermi V., Regulska E., Wolfram A. *Chem. Eur. J.*, **2022**, *28*, e202104535.

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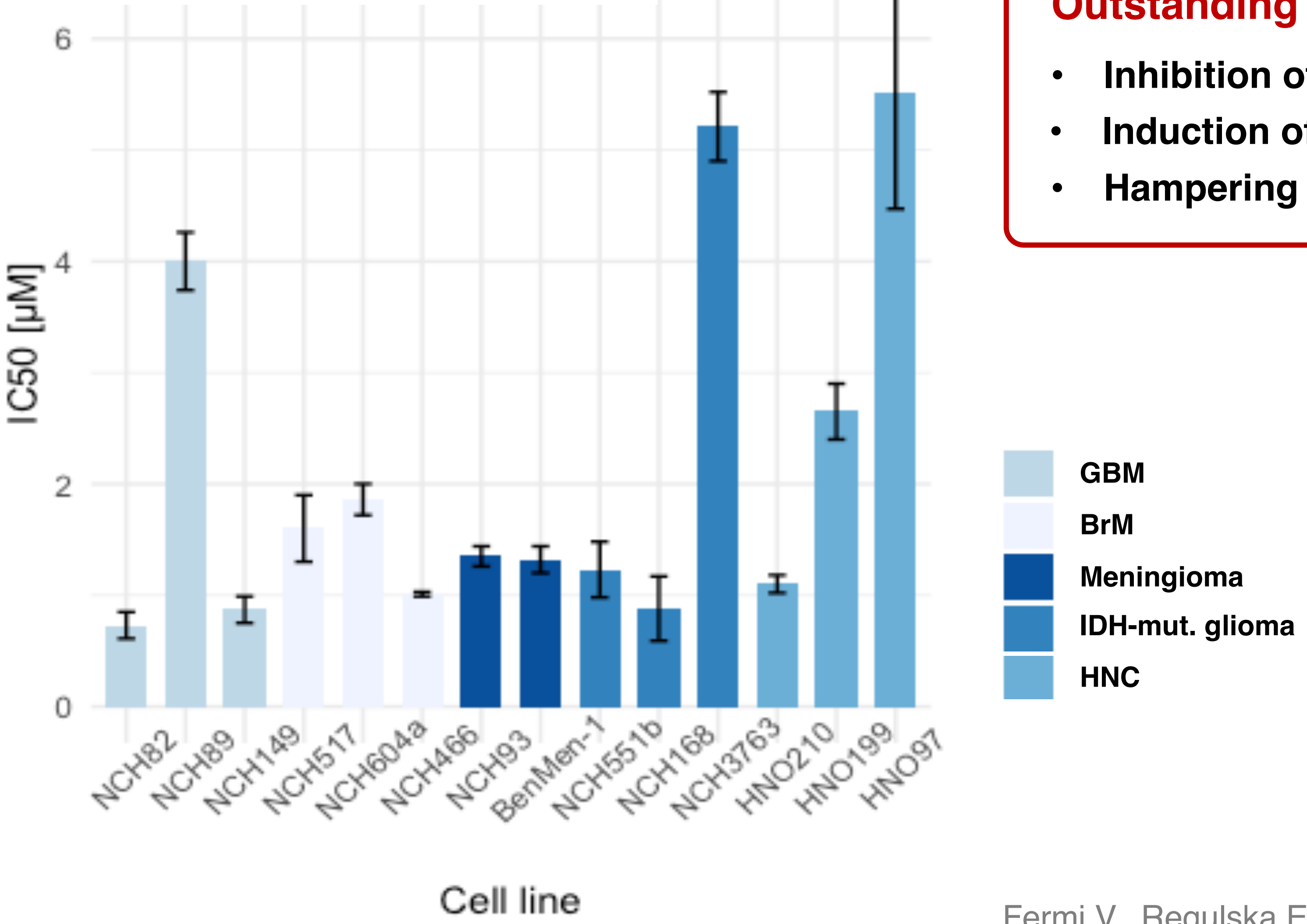
Preliminary *in vitro* findings



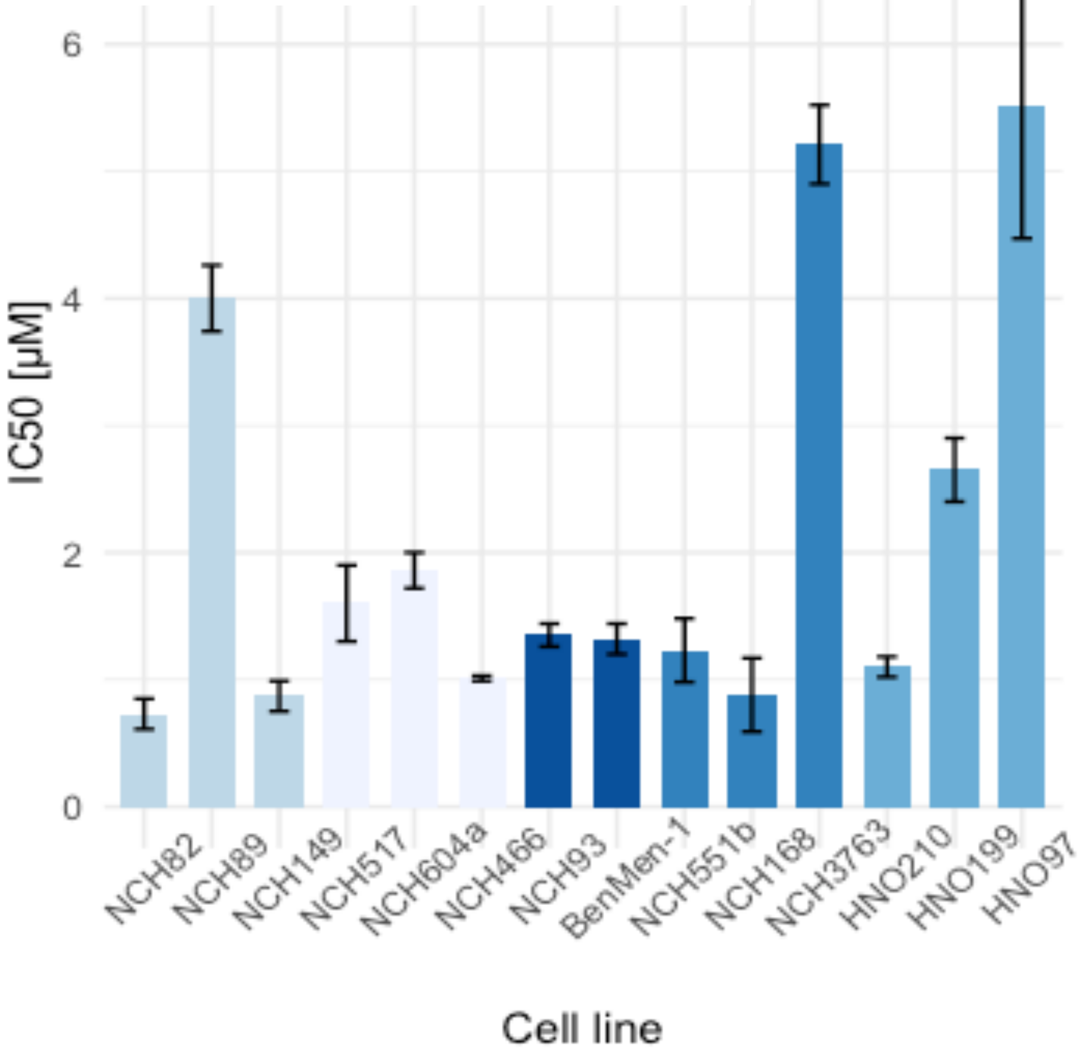
Outstanding potency in 14 cancer cell lines

- Inhibition of proliferation
- Induction of apoptosis
- Hampering cell migration

Fermi V., Regulska E., Wolfram A. *Chem. Eur. J.* **2022**, *28*, e202104535.

UCLM

Preliminary *in vitro* findings



Outstanding potency in 14 cancer cell lines

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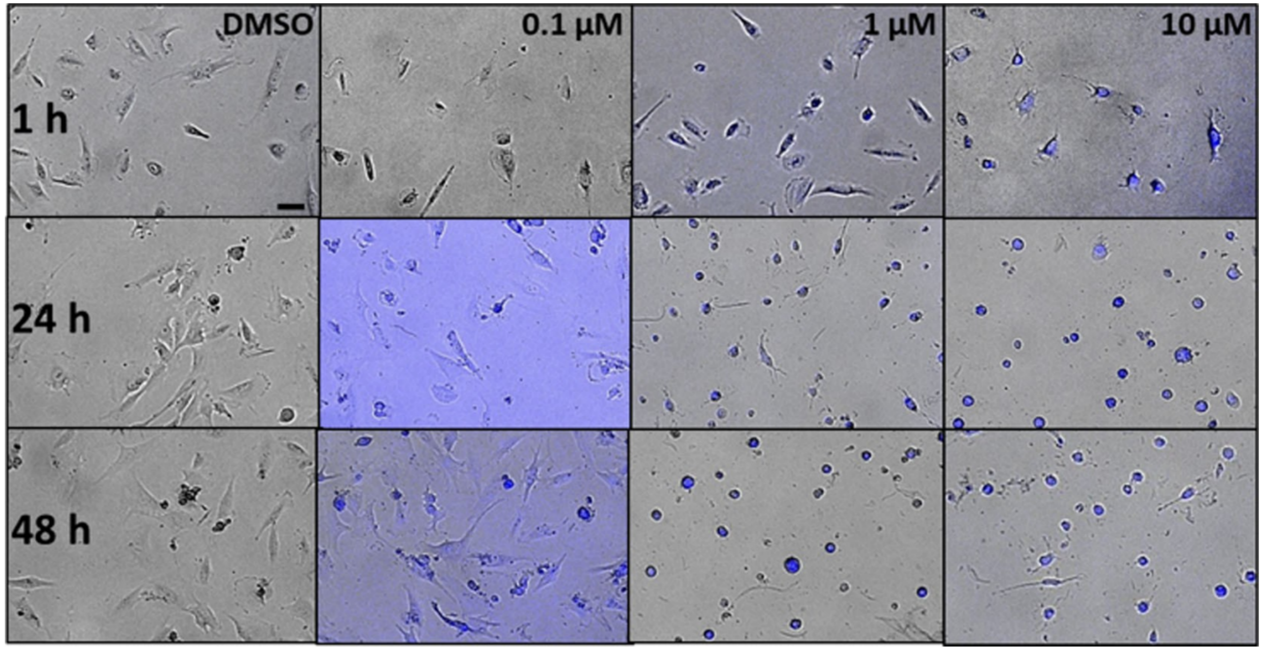
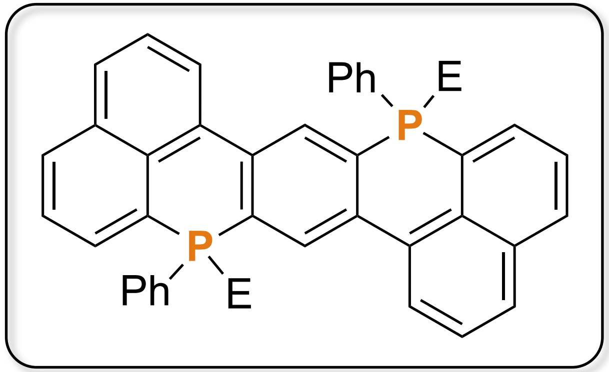
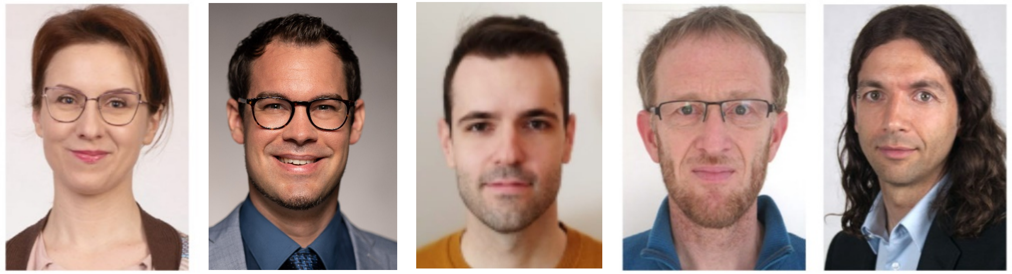
Spectroscopic properties for theranostics



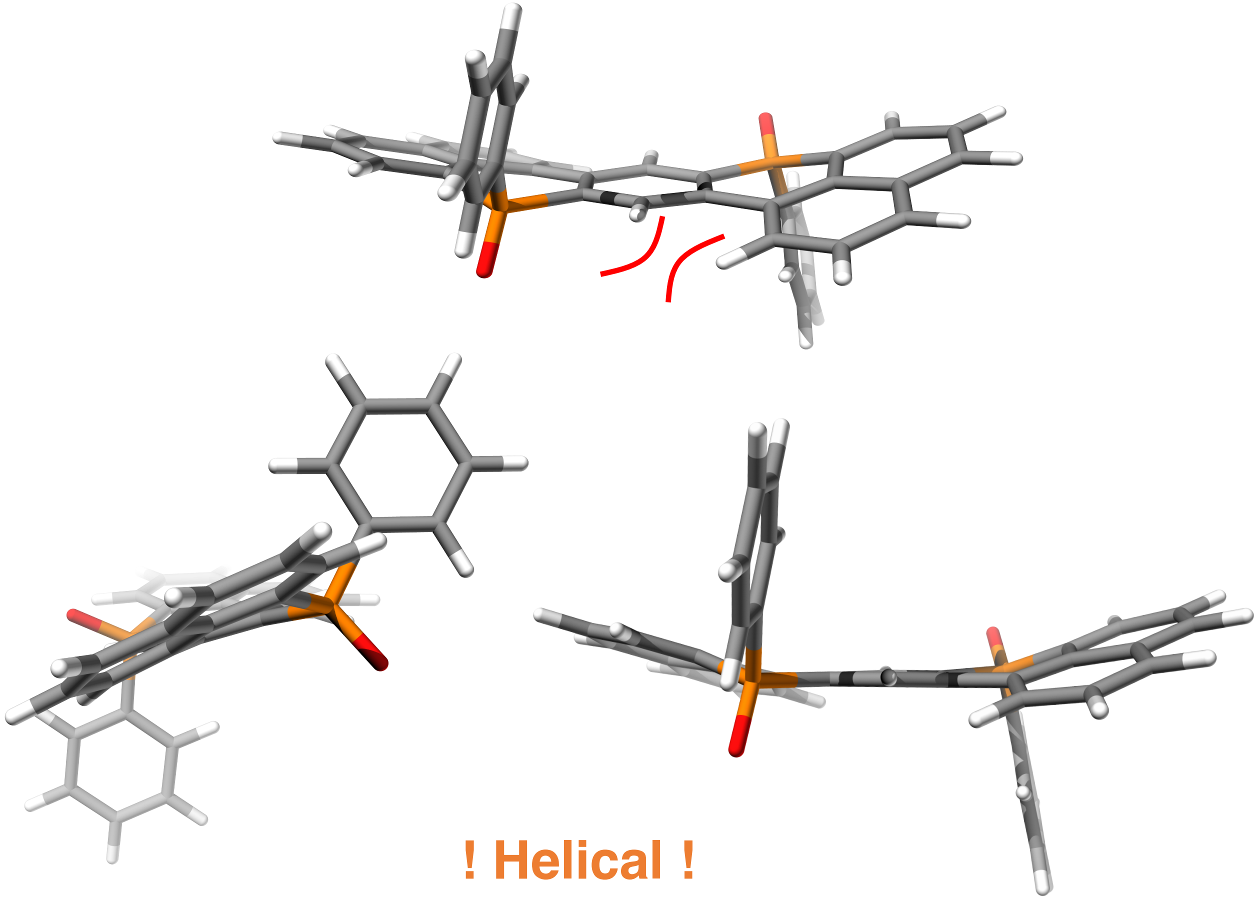


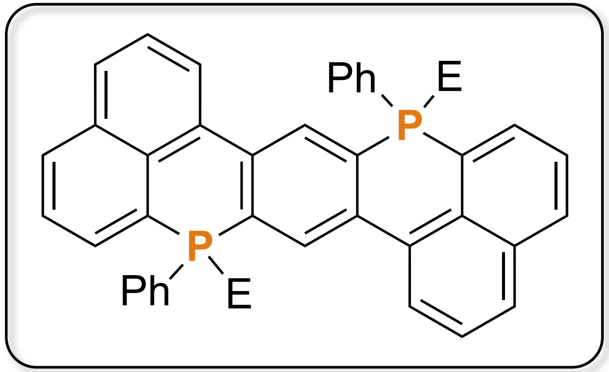
Diphosphapentaarenes



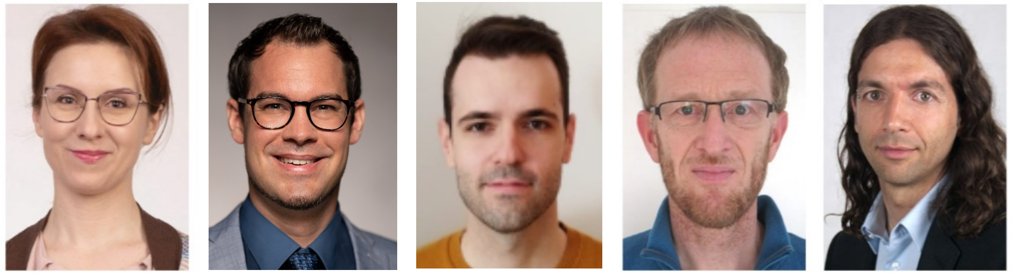
Elzbieta Regulska | Philip Hindenberg | Adrián Espiñeira Gutiérrez | Frank Rominger | Carlos Romero-Nieto

Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19





Diphosphapentaarenes



! Helical !

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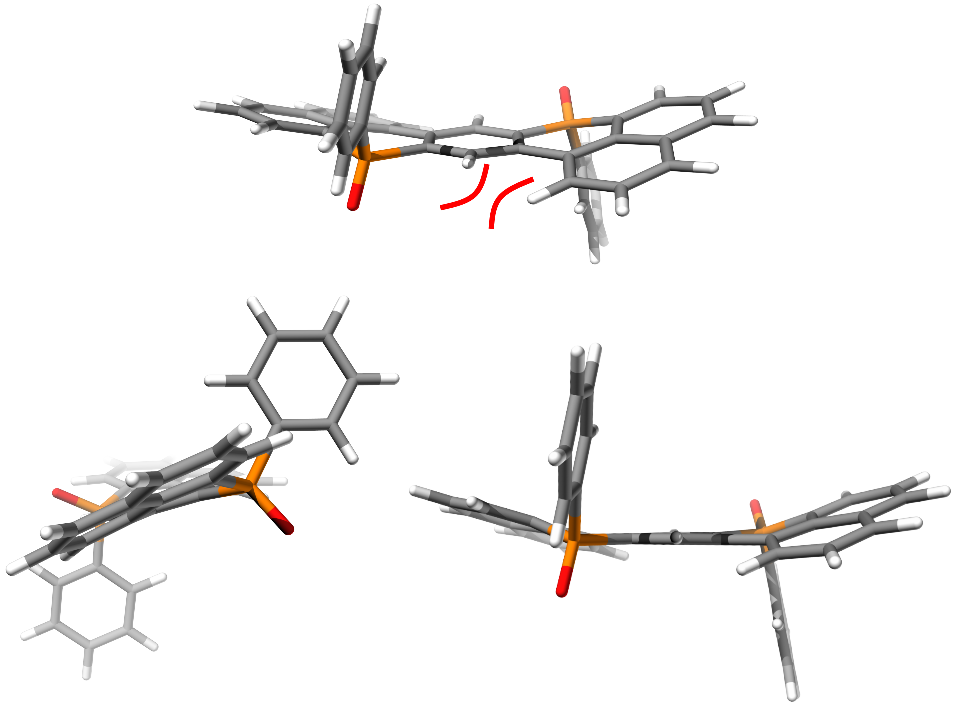
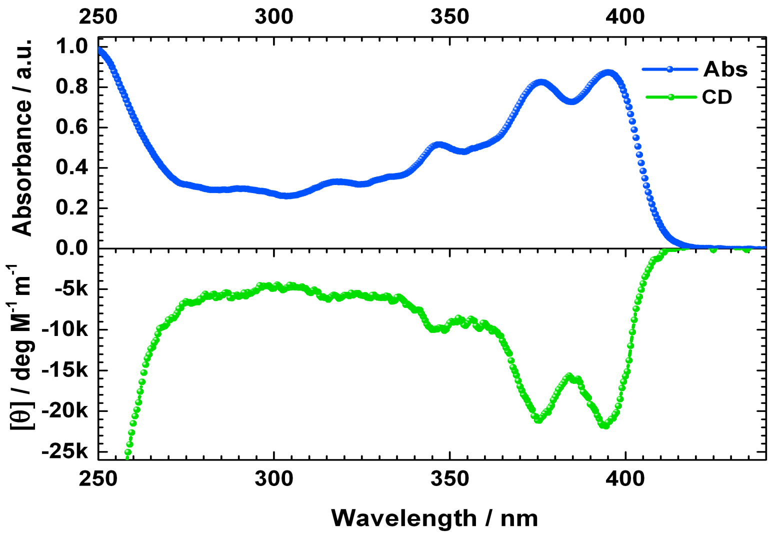


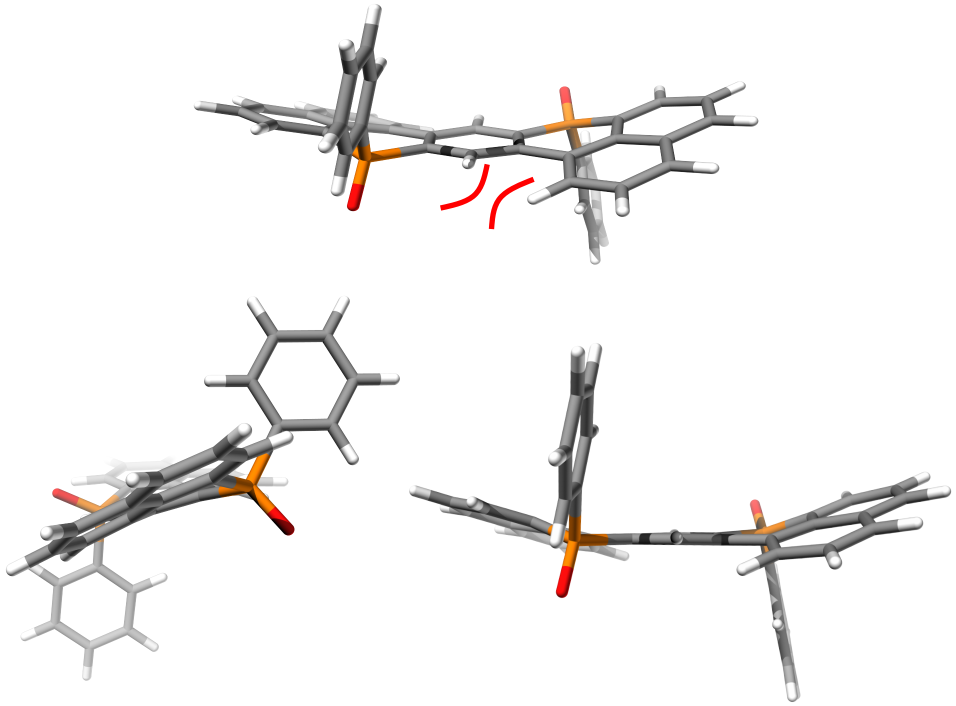


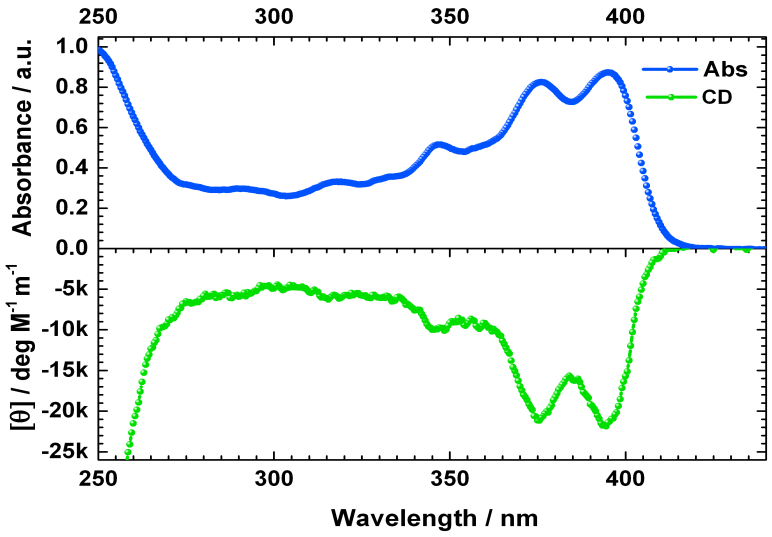
Negative Cotton effect

Maximum ellipticity of - 6.3 mDeg

Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19

Application II: Harnessing phosphaphenalenes for advanced organic materials





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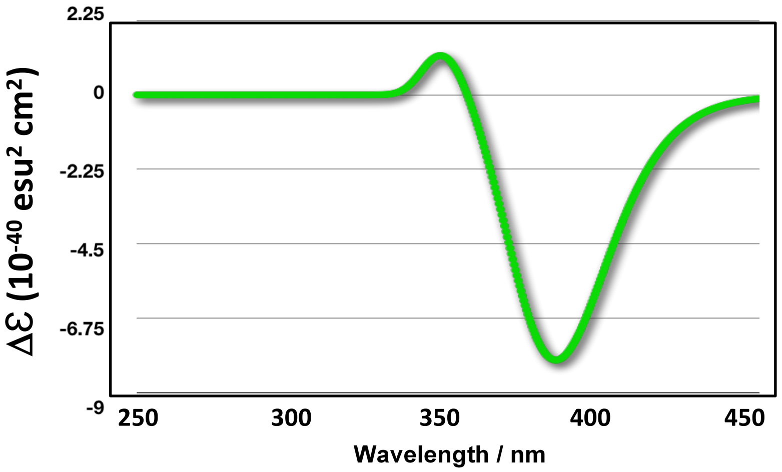
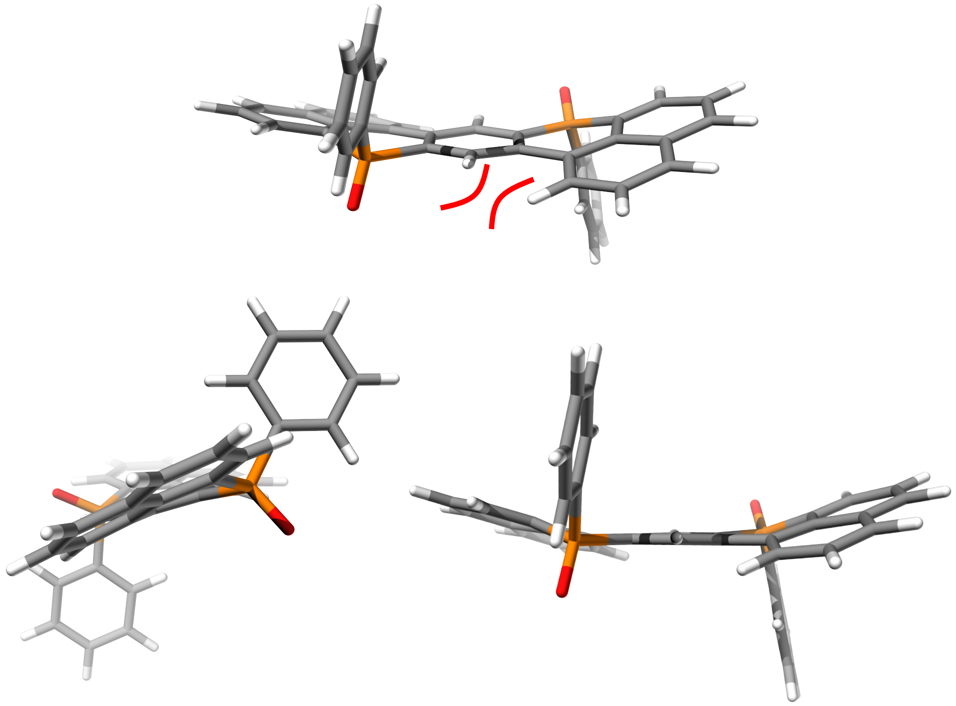


DFT Calculations at the TD-DFT-B3LYP/6-311G* level of theory

Linearly-fused arenes exhibit chiroptical activity !

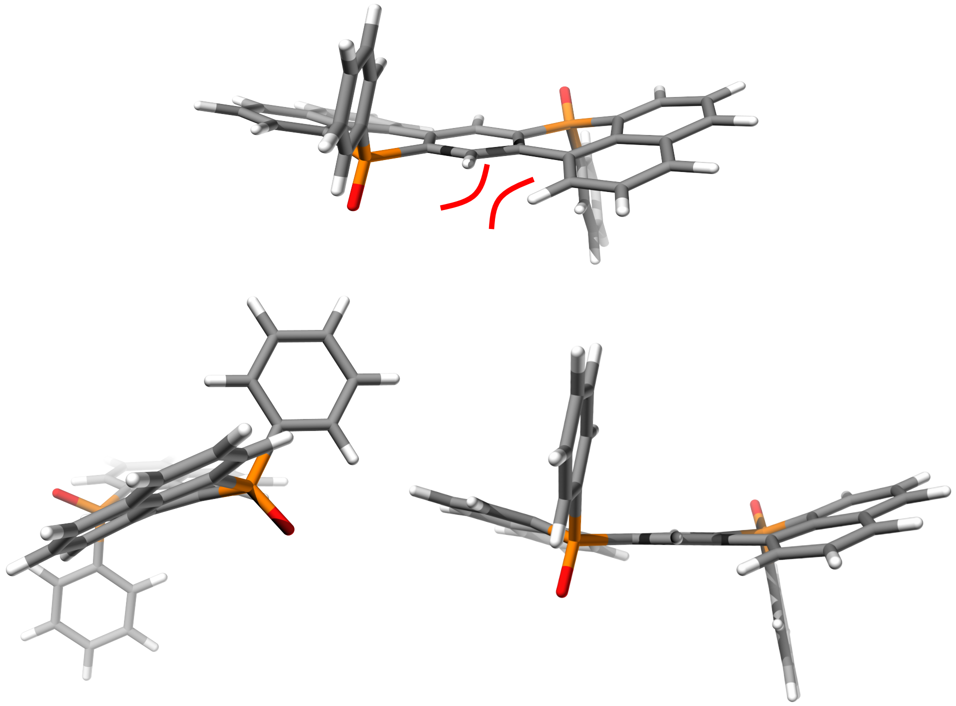
Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19



Applications of chiroptical compounds

Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19

Application II: Harnessing phosphaphenalenes for advanced organic materials

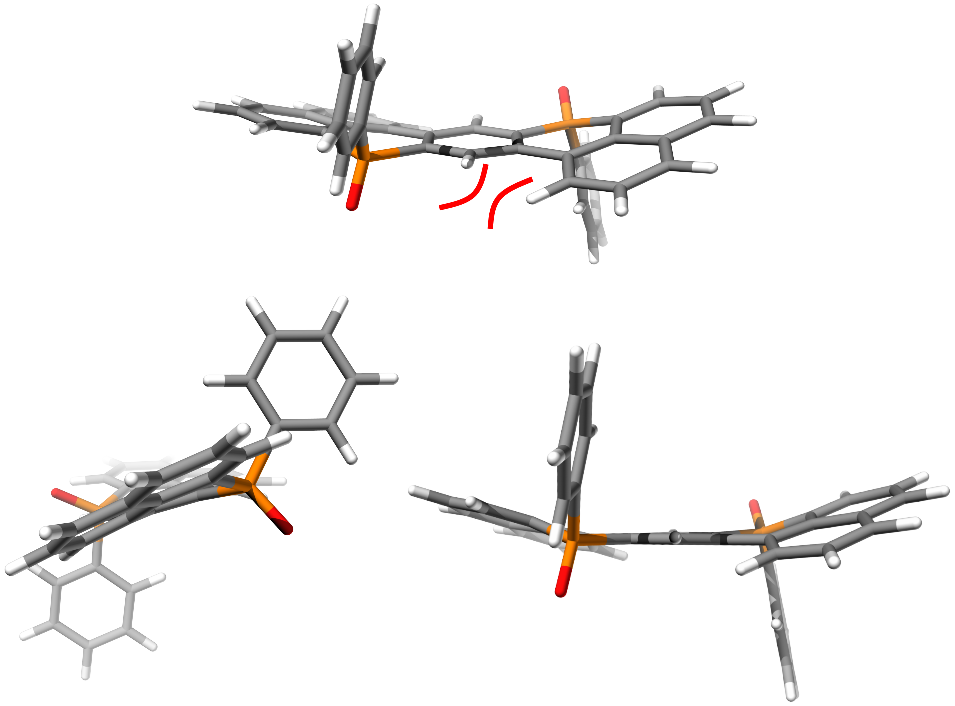


Applications of chiroptical compounds

Materials science

Catalysts

Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19



Applications of chiroptical compounds

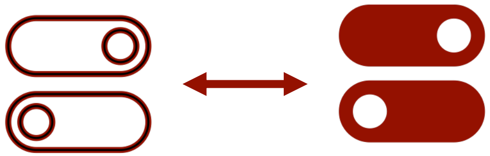
Materials science

Catalysts

Optoelectronic devices

- Telecommunication laser
- Blue laser
- Optical fibre
- LED traffic lights
- Photodiodes and solar cells

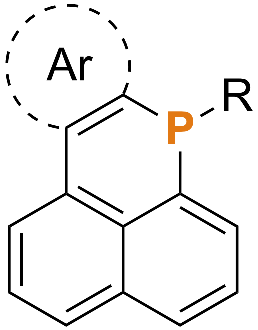
Chiroptical switches



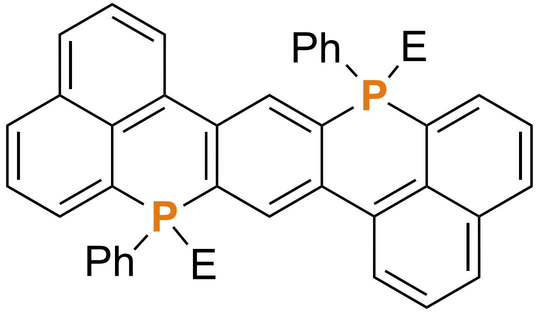
- HOT topic !
- Application in (bio)-sensor

Regulska, E. *Chem. Eur. J.* **2022**. Special issues ISNA19

Conclusion: We are at the forefront of rational chemical design

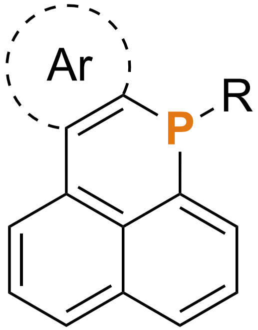


Phosphaphenalene



Diphosphapentaarenes

Conclusion: We are at the forefront of rational chemical design



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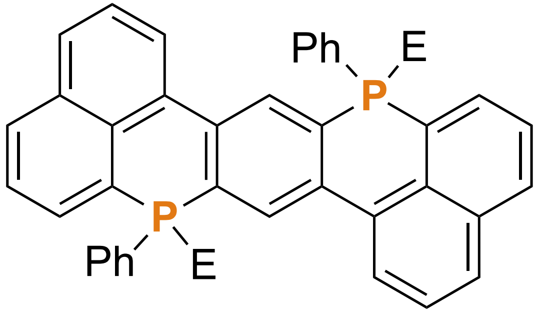

Diphosphapentaarenes

Design platform

Unique systems to develop materials with diverse applications.

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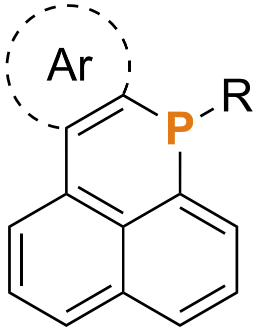
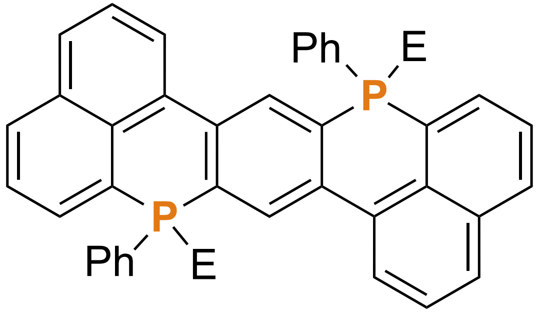


Phosphaphenalene



Diphosphapentaarenes

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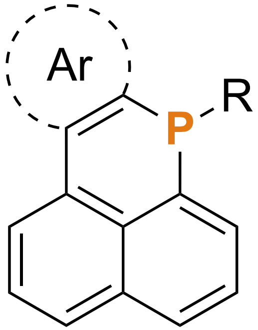
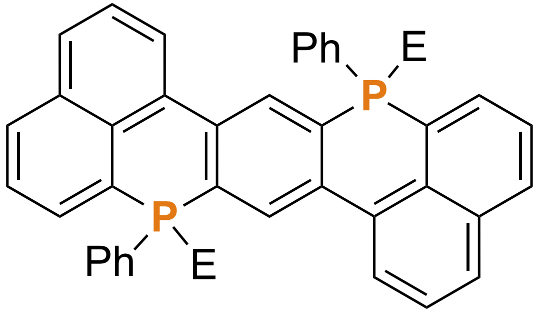
Abundant Opportunities

Myriad of possibilities to influence material & medicinal chemistry.



Phosphaphenalene



Diphosphapentaarenes

Design platform

Unique systems to develop materials with diverse applications.

Abundant Opportunities

Myriad of possibilities to influence material & medicinal chemistry.

Ongoing Advancement

A dynamic field where daily breakthroughs are still within reach.

Acknowledgment

C. Romero-Nieto Research Group

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Adrian Espiñeria Gutiérrez
Pablo Fuentes Soriano
Inés Margaret Caro Noakes
Daniel Montes Alvarez
Pablo Ruiz Vélez
Steffen Schauerte

CONTACT US

www.romero-nieto.com

@cromeronieto

@AnnaWolfram3

Bio-application


Valentina Fermi


Elzbieta Regulska


Anna Wolfram


Patrick Wessling


Frank Rominger


Christel Herold-Mende


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erc
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