

Potential New Inhibitor Molecules for SARS-CoV-2 PLpro: An In Silico and Synthetic Approach

G. Sabadini, D. Cabezas, M. Mellao, J. Mella

1 Organic Chemistry Laboratory, Institute of Chemistry and Biochemistry, Faculty of Sciences, University of Valparaíso. Gran Bretaña 1111, Playa Ancha, Valparaíso, Chile;

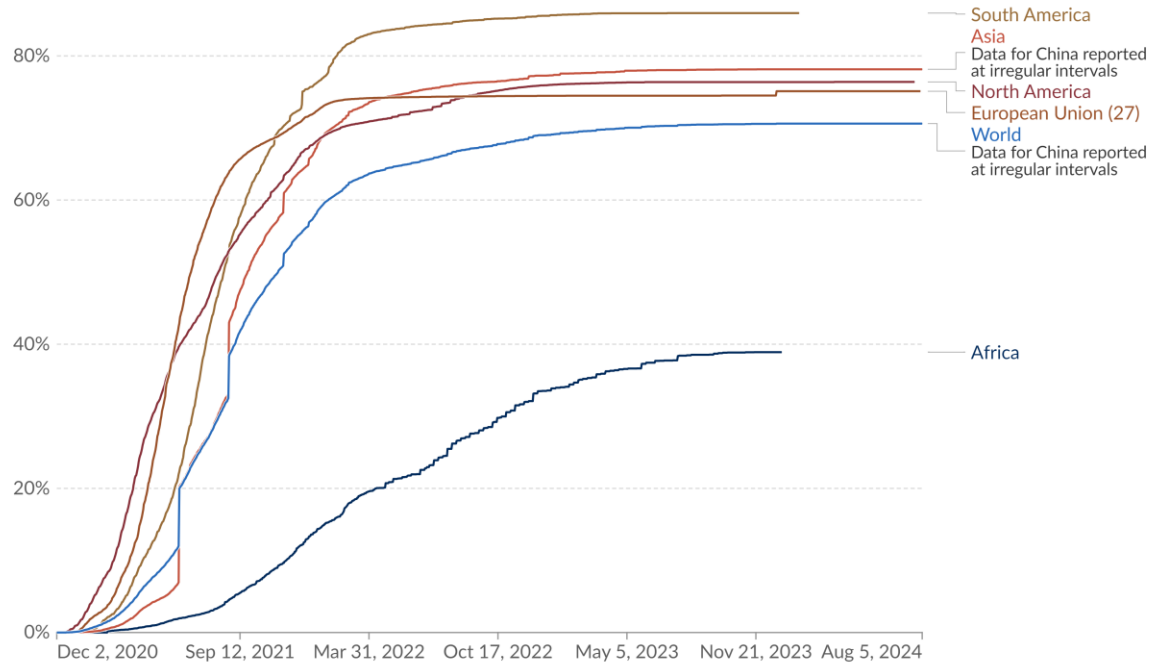
2 Institute of Research and Postgraduate Studies, Faculty of Medicine and Health Sciences, Central University of Chile, Santiago, Chile.

One problem that has not been fully resolved

Share of people who received at least one dose of COVID-19 vaccine

Total number of people who received at least one vaccine dose, divided by the total population of the country.

Our World in Data



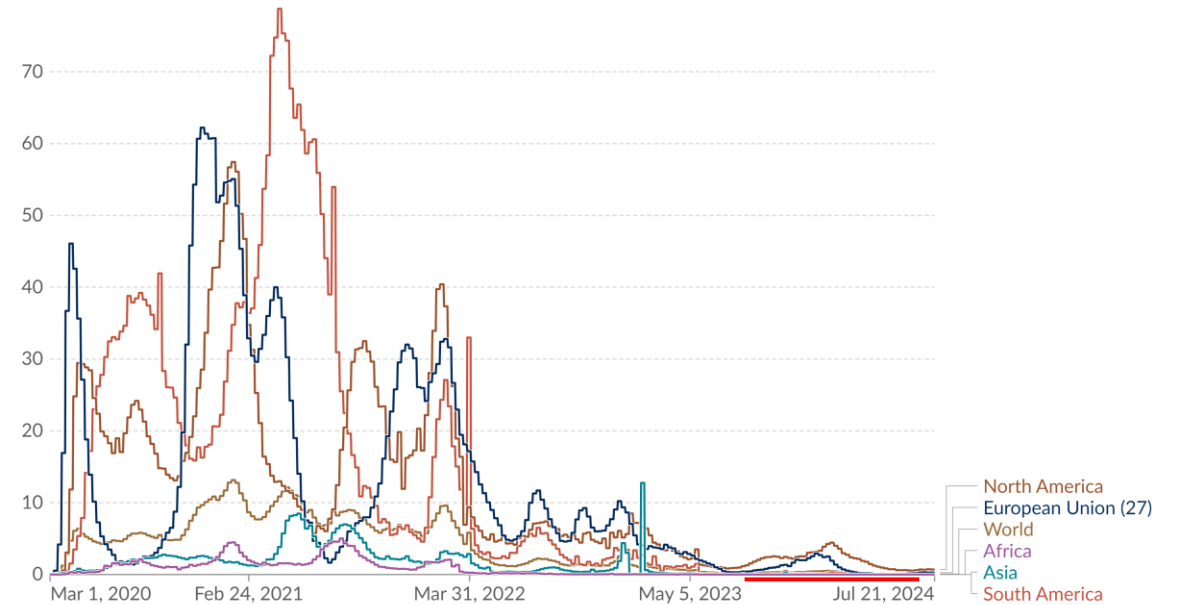
Data source: Official data collated by Our World in Data

CC BY

Weekly confirmed COVID-19 deaths per million people

Weekly confirmed deaths refer to the cumulative number of confirmed deaths over the previous week. Due to varying protocols and challenges in the attribution of the cause of death, the number of confirmed deaths may not accurately represent the true number of deaths caused by COVID-19.

Our World in Data



Data source: WHO COVID-19 Dashboard

CC BY

Edouard Mathieu, Hannah Ritchie, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Joe Hasell, Bobbie Macdonald, Saloni Dattani, Diana Beltekian, Esteban Ortiz-Ospina and Max Roser (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: '<https://ourworldindata.org/coronavirus>' [Online Resource]

One problem that has not been fully resolved



- Patients in critical condition



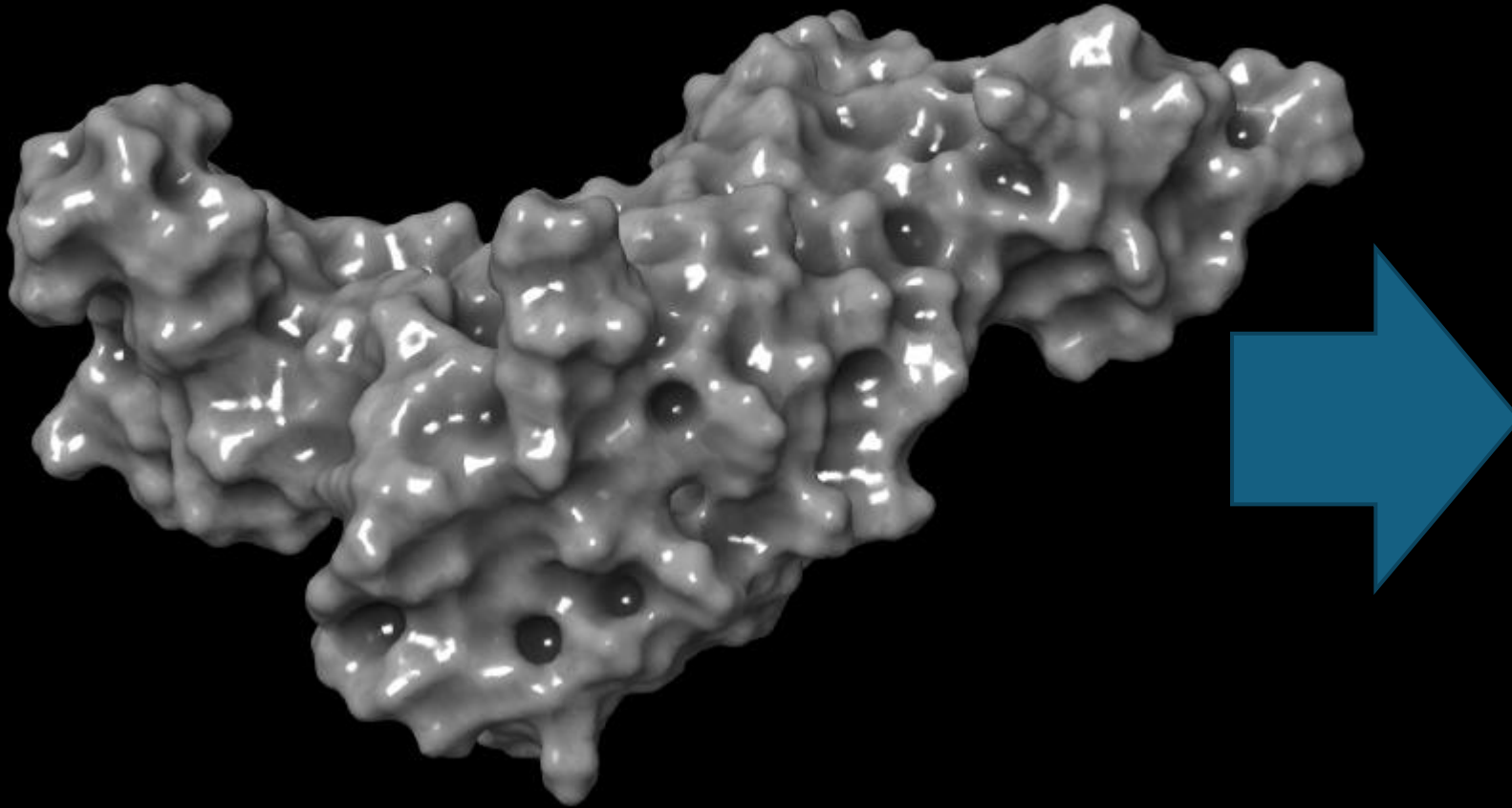
- Variants and immune escape

Does chemistry have a solution?

Drugs



PLpro function



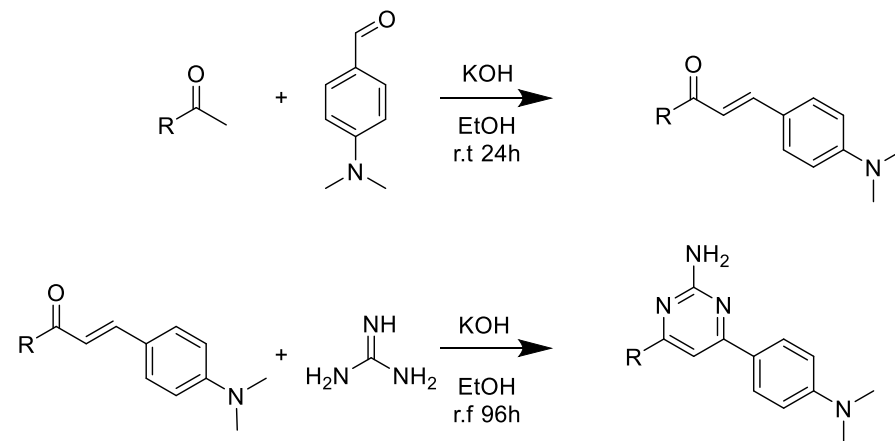
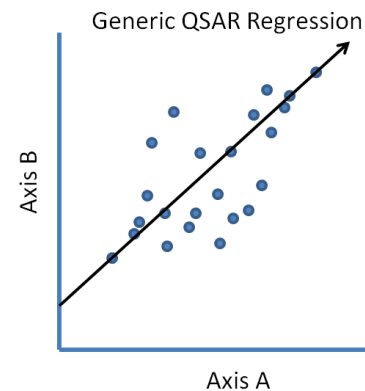
Free replication
of SARSCOV-2



Antiviral response

Research objectives

- **In silico:** Develop a new QSAR equation with internal data.
- **Synthesis:** Synthesize a molecule with high precision in the QSAR equation.



2D QSAR Methodology

113 molecules

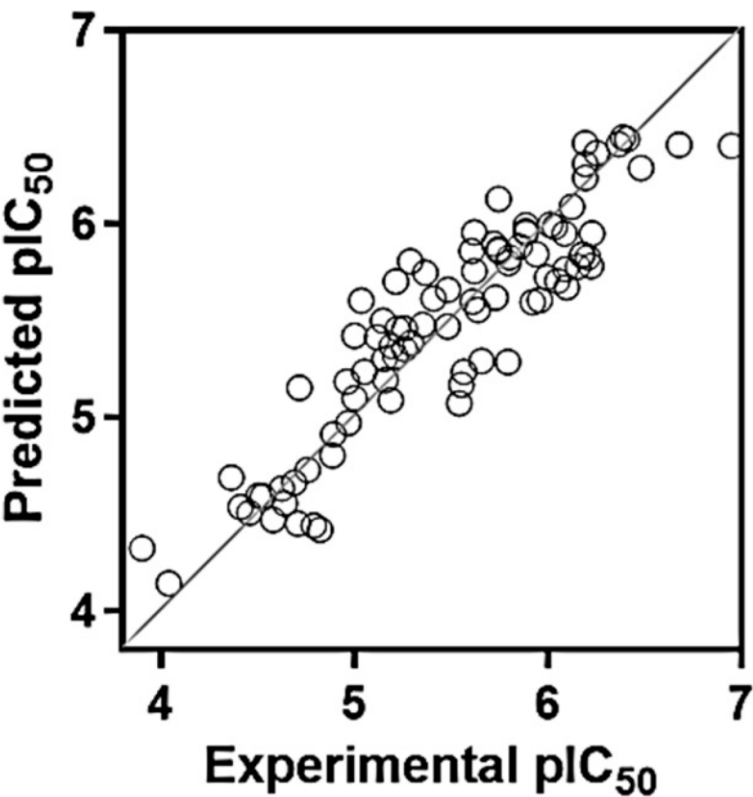
12 papers



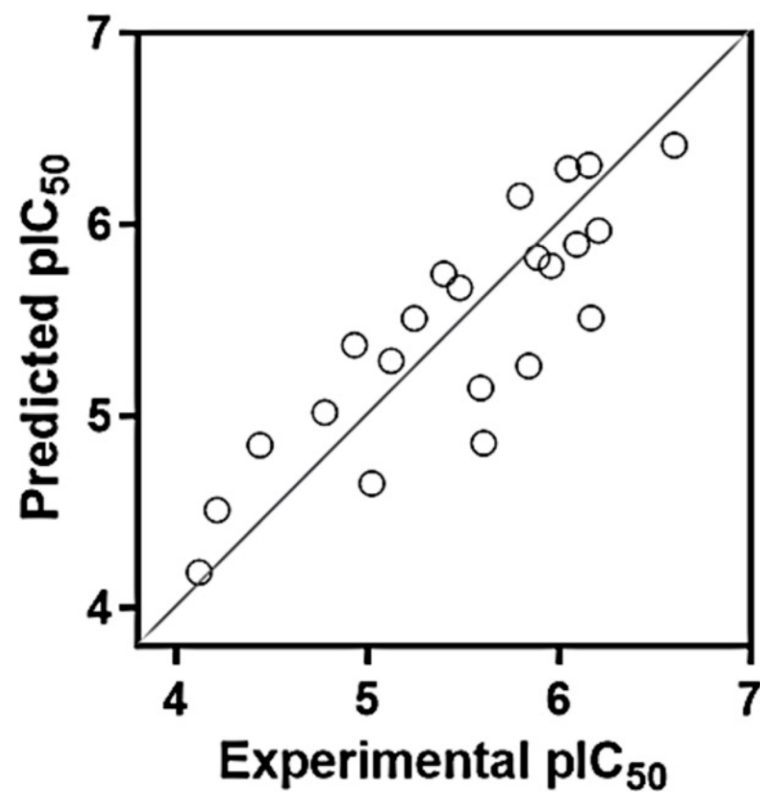
Pred
*pIC*₅₀

QSAR Results

(A) QSAR 2D Training



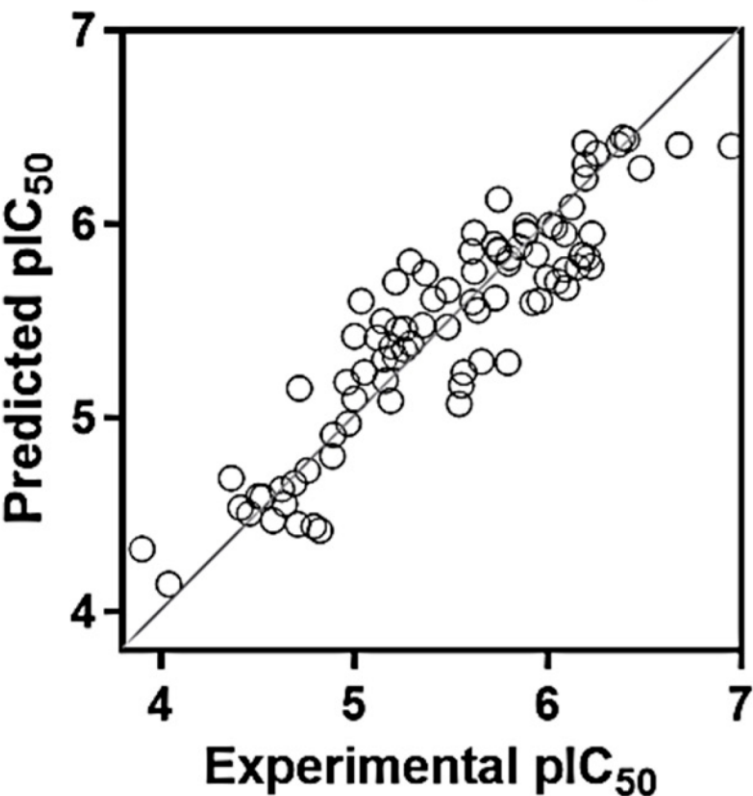
(B) QSAR 2D Test



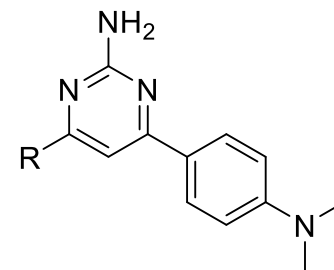
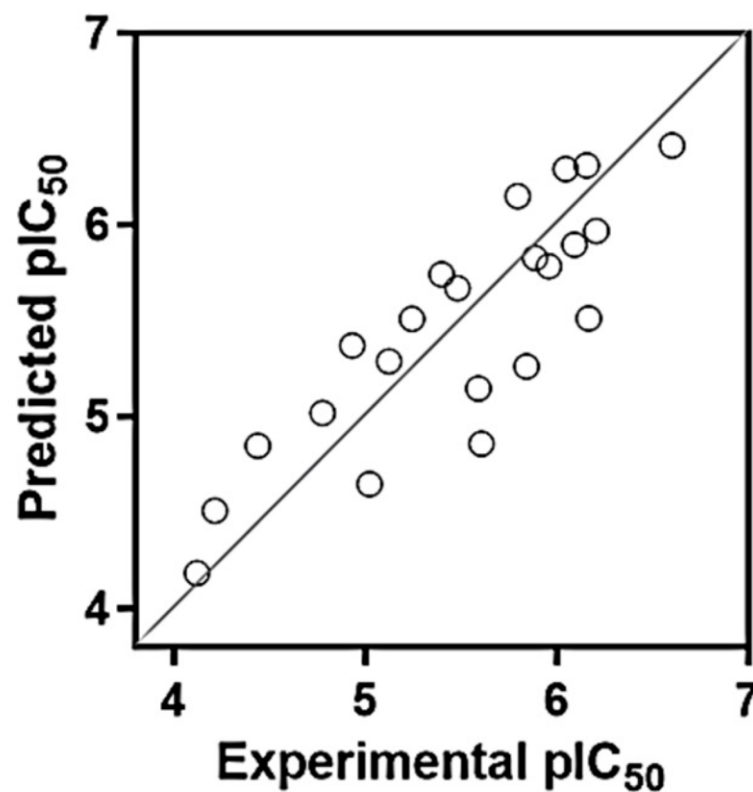
Parameter	Result
r^2	0.8333
q^2	0.770
MAE	0.237
r^2_{test}	0.721

QSAR Results

(A) QSAR 2D Training



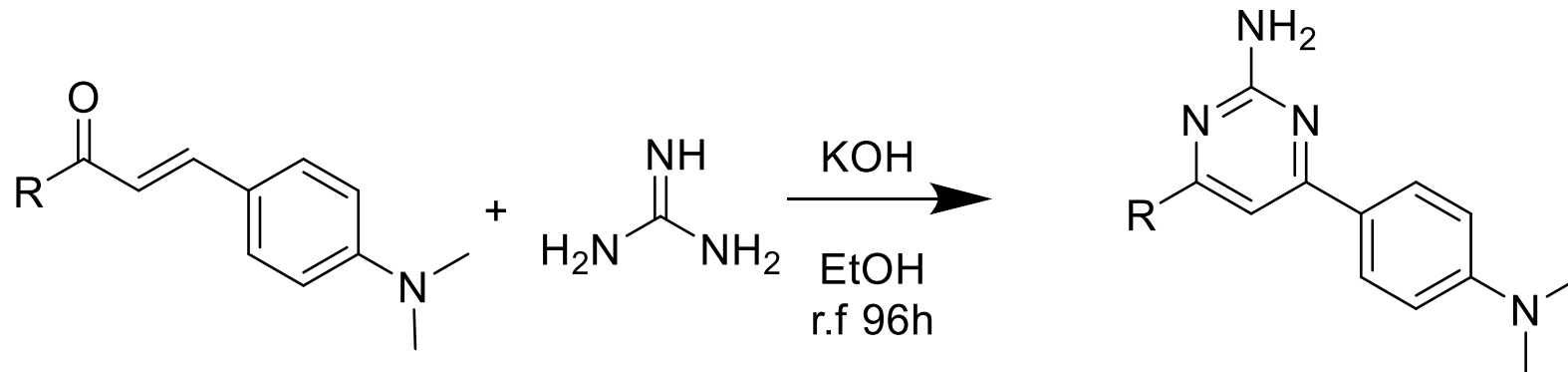
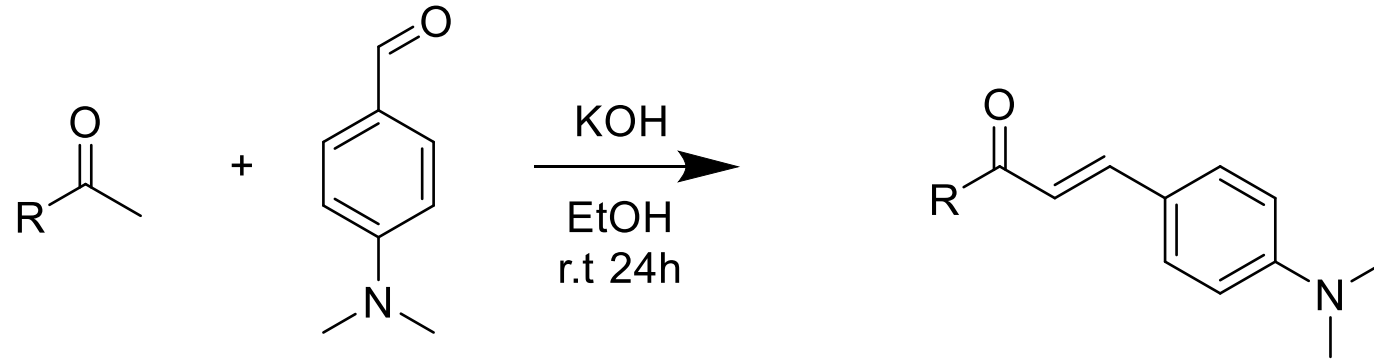
(B) QSAR 2D Test



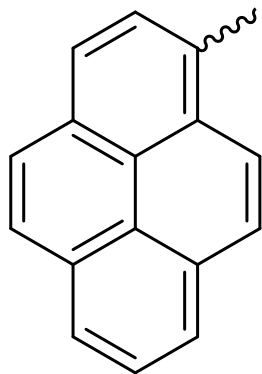
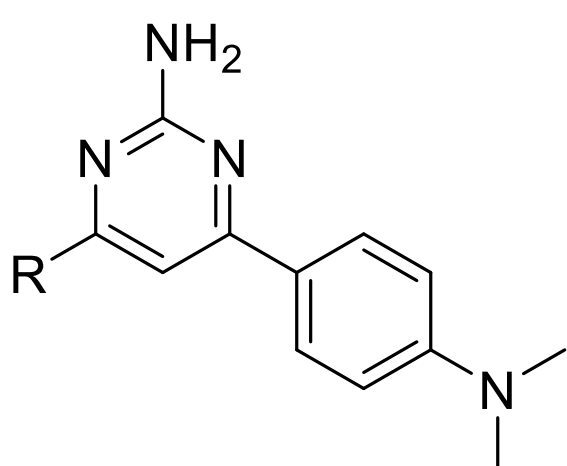
Molecule	Predicted pIC ₅₀
	8.01
	7.02

$$\text{pIC}_{50} = 3.84264 + 0.16803 \text{ ALogP} + 0.04589 \text{ ALogp2} + 0.00796 \text{ AMR} + 0.00119 \text{ DPSA-3} + 0.2659 \text{ Aromatic Rings} + 0.17442 \text{ Basic Nitrogens} + 0.22252 \text{ nAcid} - 0.23411 \text{ nF} - 0.79971 \text{ nCl} + 0.07801 \text{ nHBD} + 0.00225 \text{ TopoPSA} + 0.00145 \text{ VABC} - 0.21961 \text{ nO}$$

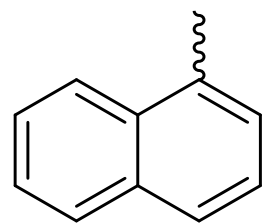
Synthesis methodology



Synthesis results

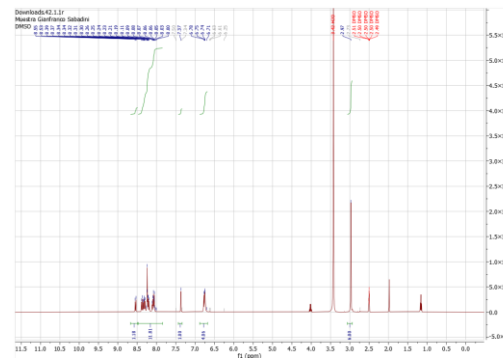


Yield=14%

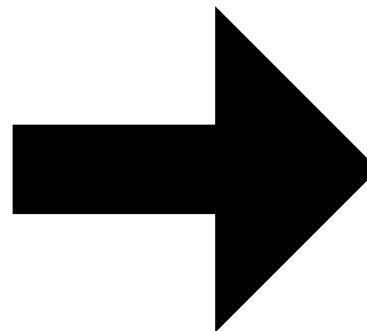
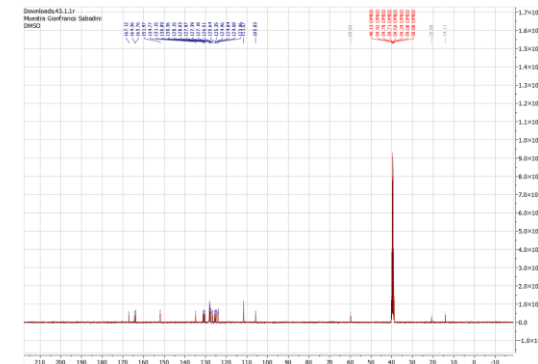


Yield=6%

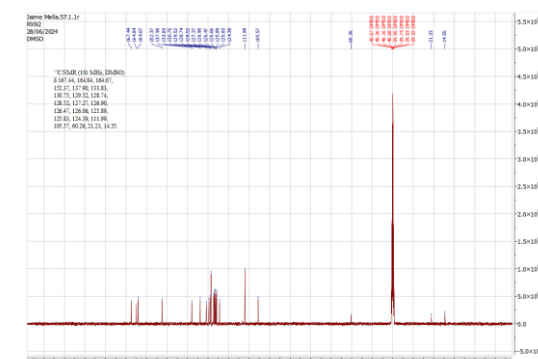
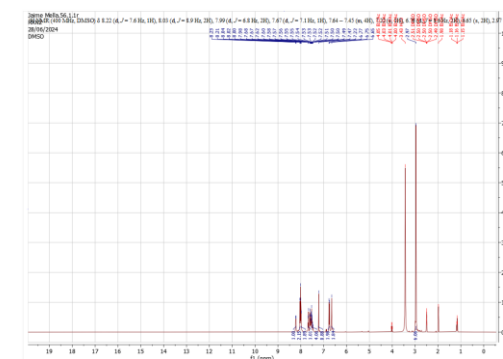
^{13}C



^1H



NMR



Conclusion

- A statistically **validated QSAR** equation was developed.
- **Two molecules** with a predicted activity **greater than 7 pIC₅₀** were identified.
- **Two potential** molecules with an **aminopyrimidine** structure were synthesized.

