

# Rational design and in-silico studies of novel potential covalent and non-covalent Fms-like tyrosine kinase 3 inhibitors. Structure-based drug design approach in targeted cancer drug discovery

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## INTRODUCTION & AIM

**Acute Myeloid Leukemia** represent only the 1.1% of all cancer diseases in the United States, on the contrary though, has one of the highest estimated mortality rates for the year 2025 [1]. While **Feline McDonough Sarcoma-like tyrosine kinase 3** was identified as a primary deregulated target, Quizartinib had been developed to specifically inhibit the inactive conformation of the kinase, nevertheless is facing tolerance due to point mutation in the Kinase Domain and Internal Tandem Duplication mutations [2].

## RESULTS & DISCUSSION

Compound	-R	Wild Type			F691L mutant		
		Score	E_conf	E_place	Score	E_conf	E_place
Quizartinib	/	-11.20	10.77	-111.87	-9.93	14.27	-115.21
Non-covalent series							
	-H	-9.31	2.66	-129.80	-8.70	-1.78	-95.70
	-tertBu	-10.27	-16.35	-43.91	-9.93	-14.70	-116.12
Covalent series							
	-H	-6.83	-81.98	-3.74	-6.45	-81.72	-5.13
	-tertBu	-8.02	-97.90	-10.42	-7.80	-90.97	-7.77

Table 1: Docking results performed on the inactive conformation of the FLT3 crystal (PDB: 4XUF). Rigid receptor, values reported in kcal/mol. Results obtained with MOE docking software [3]

Molecular docking was performed on the inactive conformation of the target (PDB: 4XUF), in order to get access to the same binding pocket exploited by Quizartinib.

### Non-covalent series

- Comparable scores to the approved drug
- Stronger interactions in the hinge and enhanced flexibility
- Synthetically more accessible

### Covalent series

- Covalent bond with Cys828 via cyano group
- Consistent results in both WT and mutant while Quizartinib showed lower score in the F691 mutant

## CONCLUSION

Considering the encouraging preliminary data, we are looking forward to harvest more data from:

- Additional *in-silico* simulations based on Molecular Dynamics
- Synthesis
- Wide and targeted *in-vitro* testing

## REFERENCES

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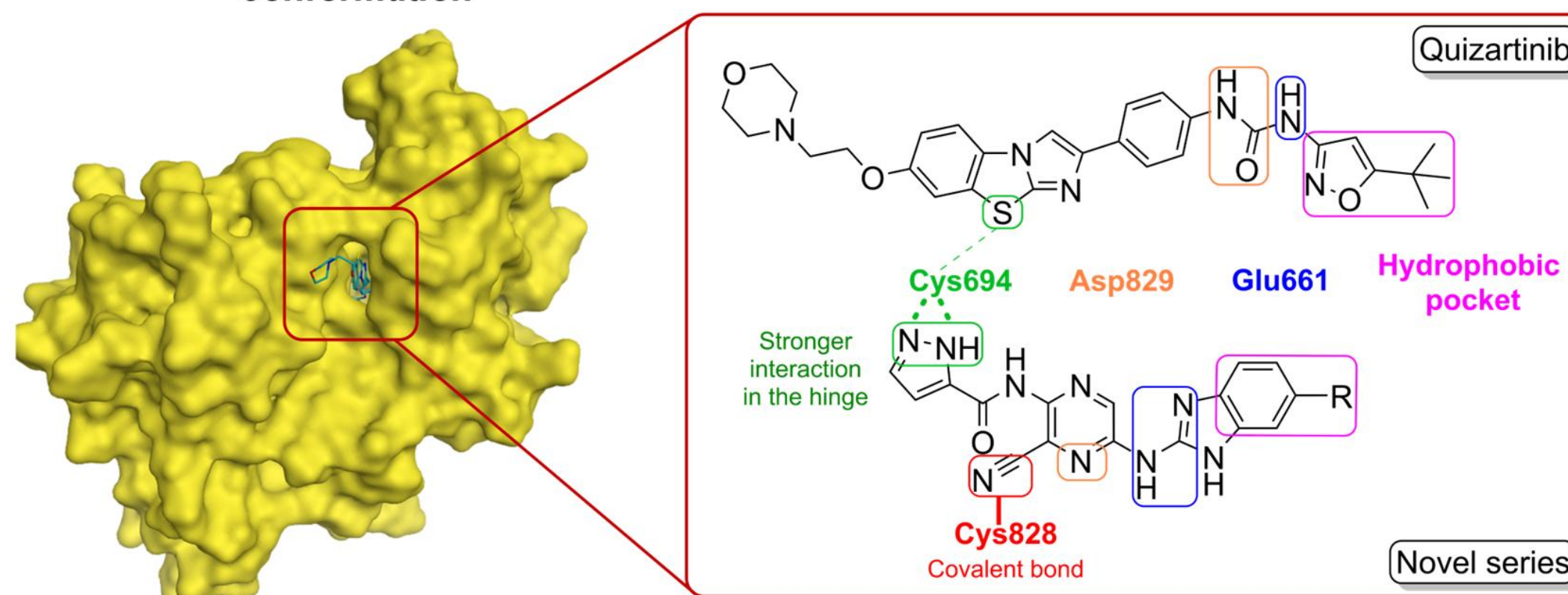
[1] SEER\*Explorer: An interactive website for SEER cancer statistic 2024

[2] Polak TB, et.al., Association of FLT3–internal tandem duplication length with overall survival in acute myeloid leukemia: a systematic review and a meta-analysis. *Haematologica*, 2022 Oct 1

[3] Molecular Operating Environment (MOE), 2024.0601 Chemical Computing Group ULC, 910-1010 Sherbrooke St. W., Montreal, QC H3A 2R7, 2025

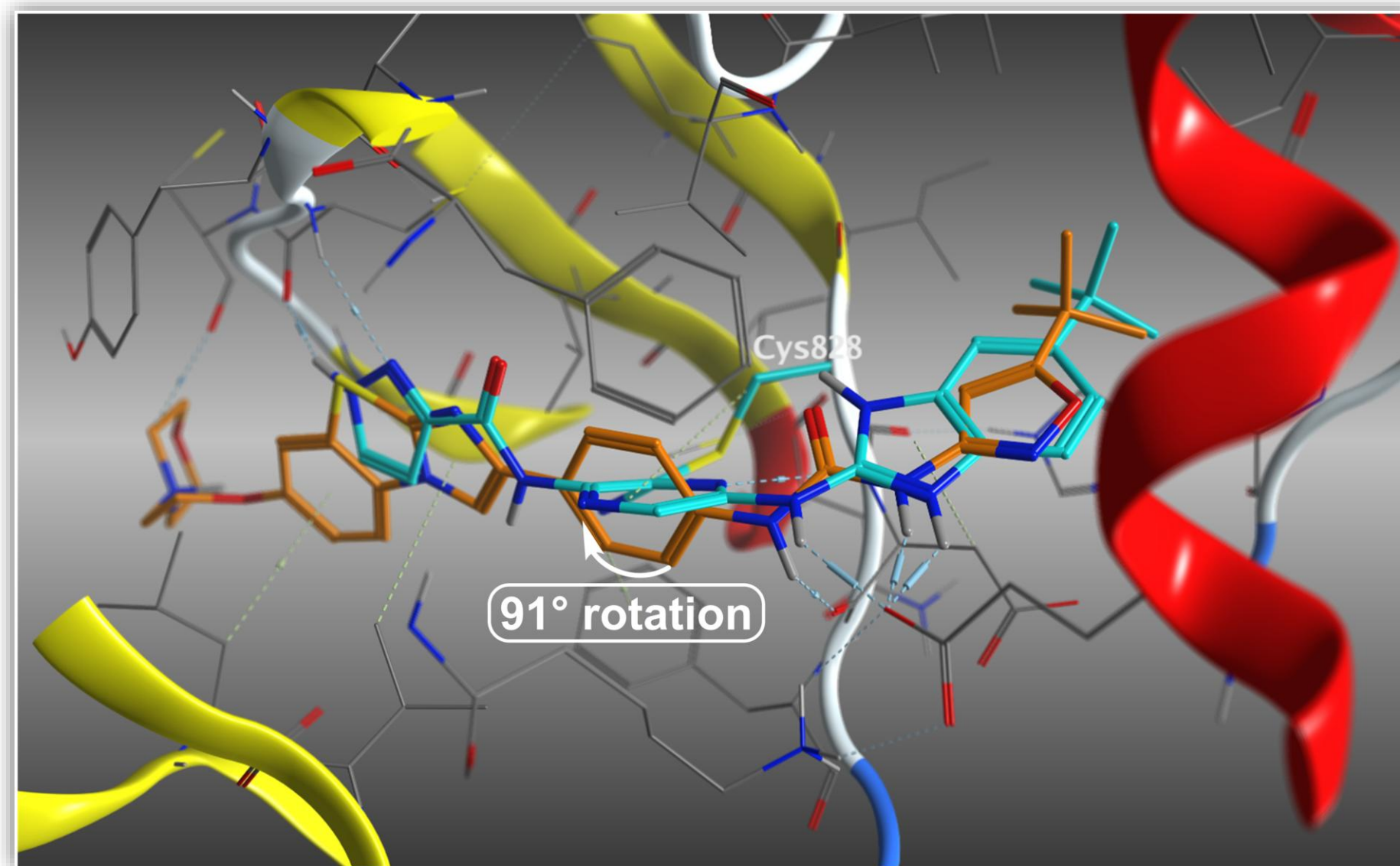
## METHOD

FLT3 DFG-out inactive conformation



In this study we used an in-silico approach to build a novel series with different heterocyclic-based compounds, more likely to withstand FLT3 mutations. We aimed at:

- **Stronger** acceptor-donor interaction with **Cys694** in the hinge
- **Isosteric replacement** of the ureido linker with a benzoimidazole moiety
- Amide bond in place of the Quizartinib's tricyclic core, better **flexibility** and synthetically more accessible
- **Covalent-binding** series in the region of the pocket where the point mutation occurs



- Quizartinib stability highly depends on the **T-shaped  $\pi$ -stacking** (absent in the mutant)
- The **Covalent series** might elude the **F691L mutation** due to a different orientation of the plane where the Pyrazine ring lays, hence the series does not depend on the **H- $\pi$**  interaction in the WT and therefore shouldn't be affected by the point mutation
- Poses are kept in place by an Acceptor-Donor interaction between Asp829 and Pyrazine's Nitrogen in position 1

