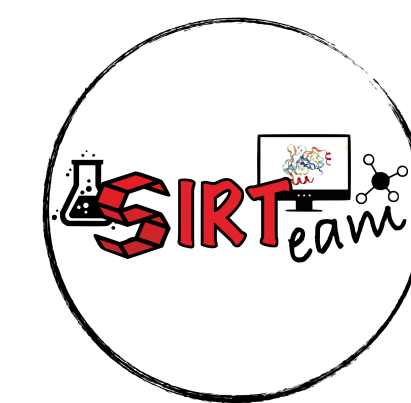


DISCOVERY OF DUAL NNMT/COX-2 INHIBITORS THROUGH INTEGRATED STATIC & DYNAMIC PHARMACOPHORE-BASED VIRTUAL SCREENING

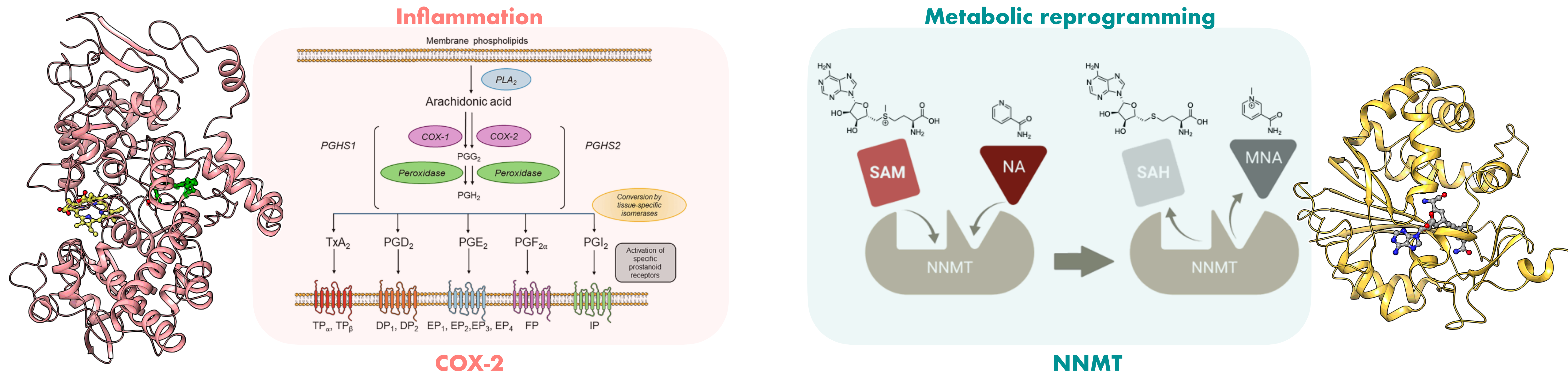


Habibe Beyza GUNINDI, Gokcen EREN

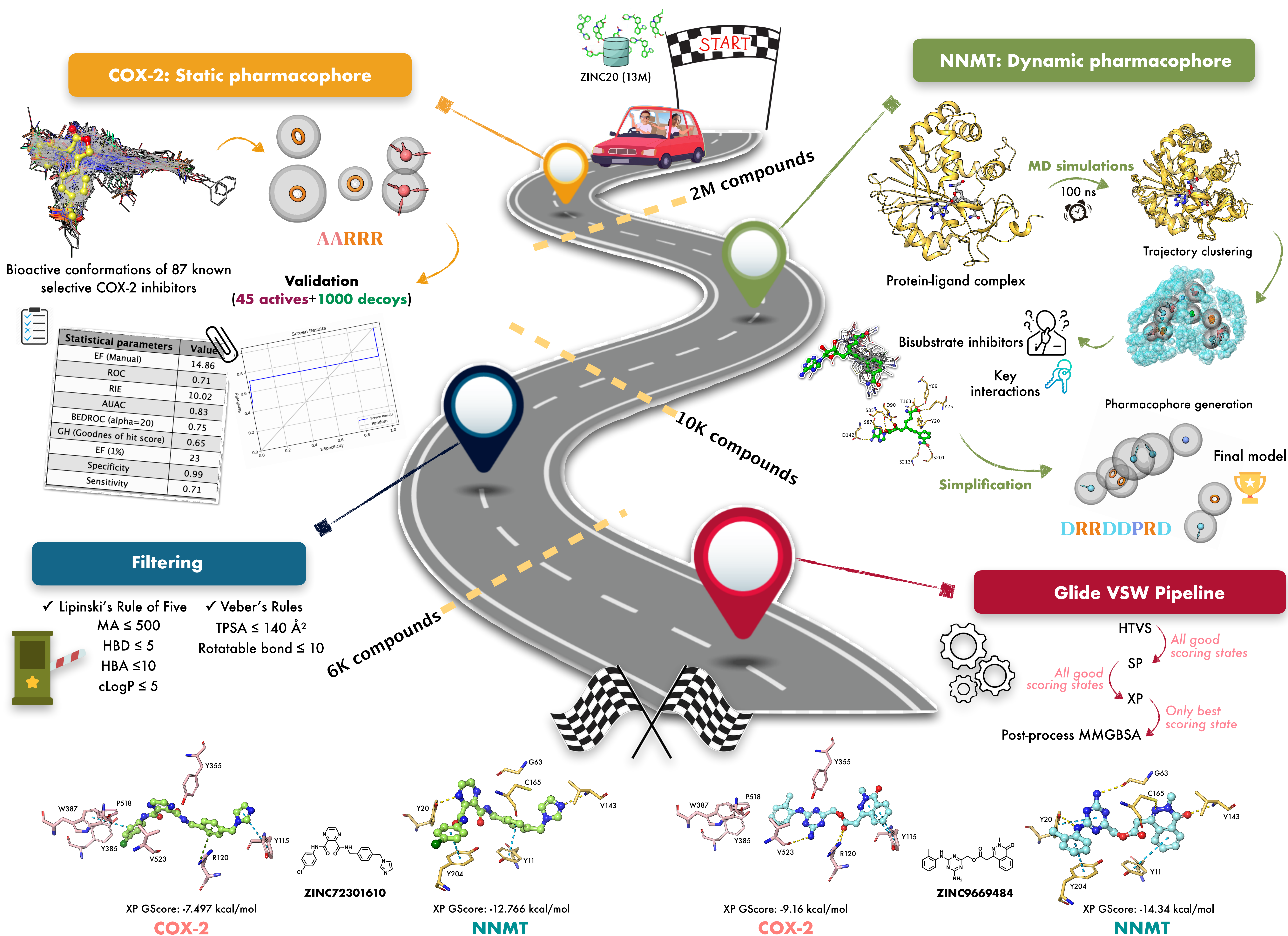
Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, SIRTeam Group, Ankara, Türkiye



Chronic inflammation and metabolic reprogramming are closely interconnected processes that contribute to cancer development and progression.¹ In this context, **nicotinamide N-methyltransferase (NNMT)** has emerged as an important metabolic regulator linking altered nicotinamide metabolism to tumor promoting phenotypes.² NNMT catalyzes the S-adenosyl-L-methionine (SAM) dependent methylation of nicotinamide and other pyridines, generating 1-methylnicotinamide (MNA) and the corresponding pyridinium ions. Beyond its traditional role in nicotinamide metabolism and detoxification, NNMT is overexpressed in various malignancies and has been associated with tumor cell proliferation, migration, epithelial-mesenchymal transition (EMT), and therapeutic resistance, highlighting its potential as a promising anticancer target.³⁻⁵ **Cyclooxygenase-2 (COX-2)** is a key mediator of inflammation and tumor progression through the production of PGE₂, promoting proliferation, invasion, EMT, and therapeutic resistance.⁶ Emerging evidence highlights both NNMT and COX-2 as promising therapeutic targets, supporting their simultaneous inhibition as a potential anticancer strategy.



Accordingly, the present study aimed to identify novel dual NNMT/COX-2 inhibitors to target the interconnected metabolic and inflammatory pathways in tumor progression.



Static and dynamic pharmacophore-based virtual screening approaches were applied for the identification of potential dual NNMT/COX-2 inhibitors. Selected compounds emerged as the most promising hits, exhibiting key interactions with both targets. These compounds represent promising starting points for further computational and experimental validation toward the development of novel dual NNMT/COX-2 inhibitors.

1. Nishida, A.; Andoh, A., Cells, **2025**, 14 (7).

2. Li, J. J.; Sun, W. D.; Zhu, X. J., et al. Metabolites, **2024**, 14 (6).

3. Li, X. Y.; Pi, Y. N.; Chen, Y., et al. Front Oncol **2022**, 12, 894744.

4. Sun, W.-D.; Zhu, X.-J.; Li, J.-J., et al. Int. Immunopharmacol., **2024**, 142, 113208.

5. Ulanovskaya, O. A.; Zuhl, A. M.; Cravatt, B. F., Nat Chem Biol **2013**, 9 (5), 300-306.

6. Jin, K.; Qian, C.; Lin, J., et al. Front Oncol **2023**, 13, 1099811.

