

Discovery of novel selective TLR7 agonists based on chromeno[3,4-d]imidazol-4(1H)-one and 2-(trifluoromethyl)quinoline/quinazoline-4-amine scaffold

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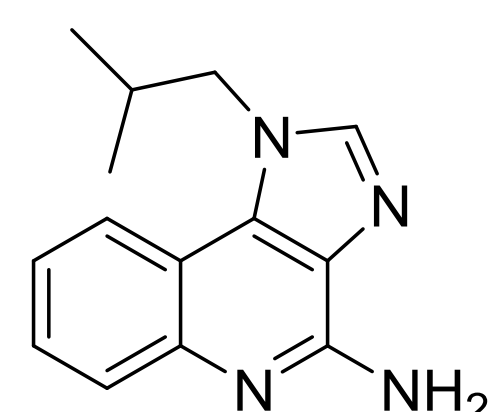
TOLL-LIKE RECEPTORS (TLRs) AS TARGETS

13 types

Intracellular on endosome:

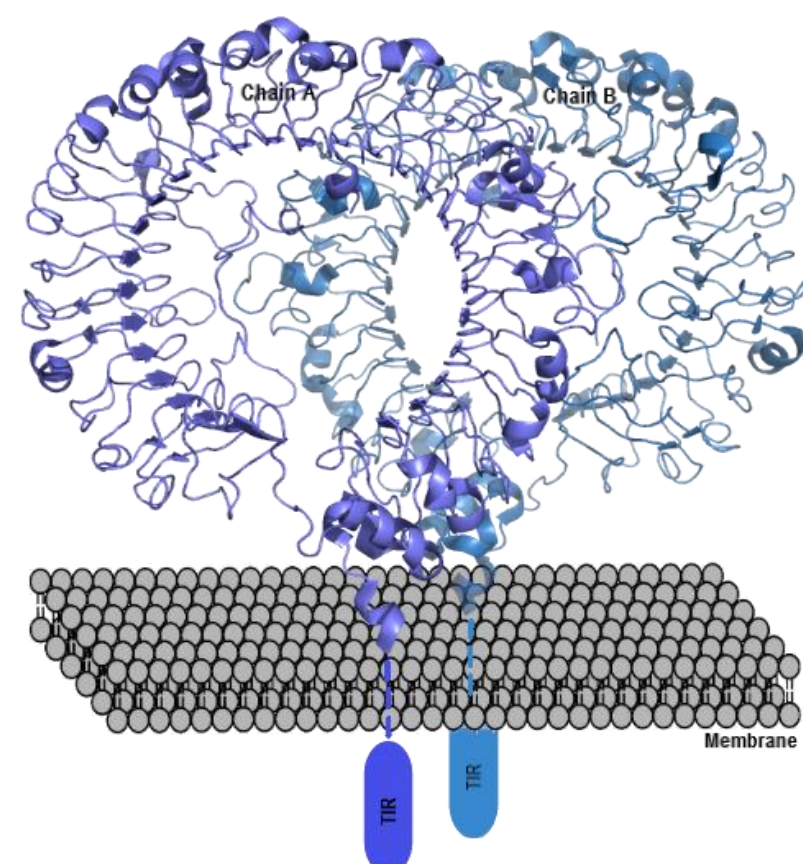
TLR3, TLR7, TLR8, TLR9

Drug on the market - TLR7 agonist IMIQUIMOD



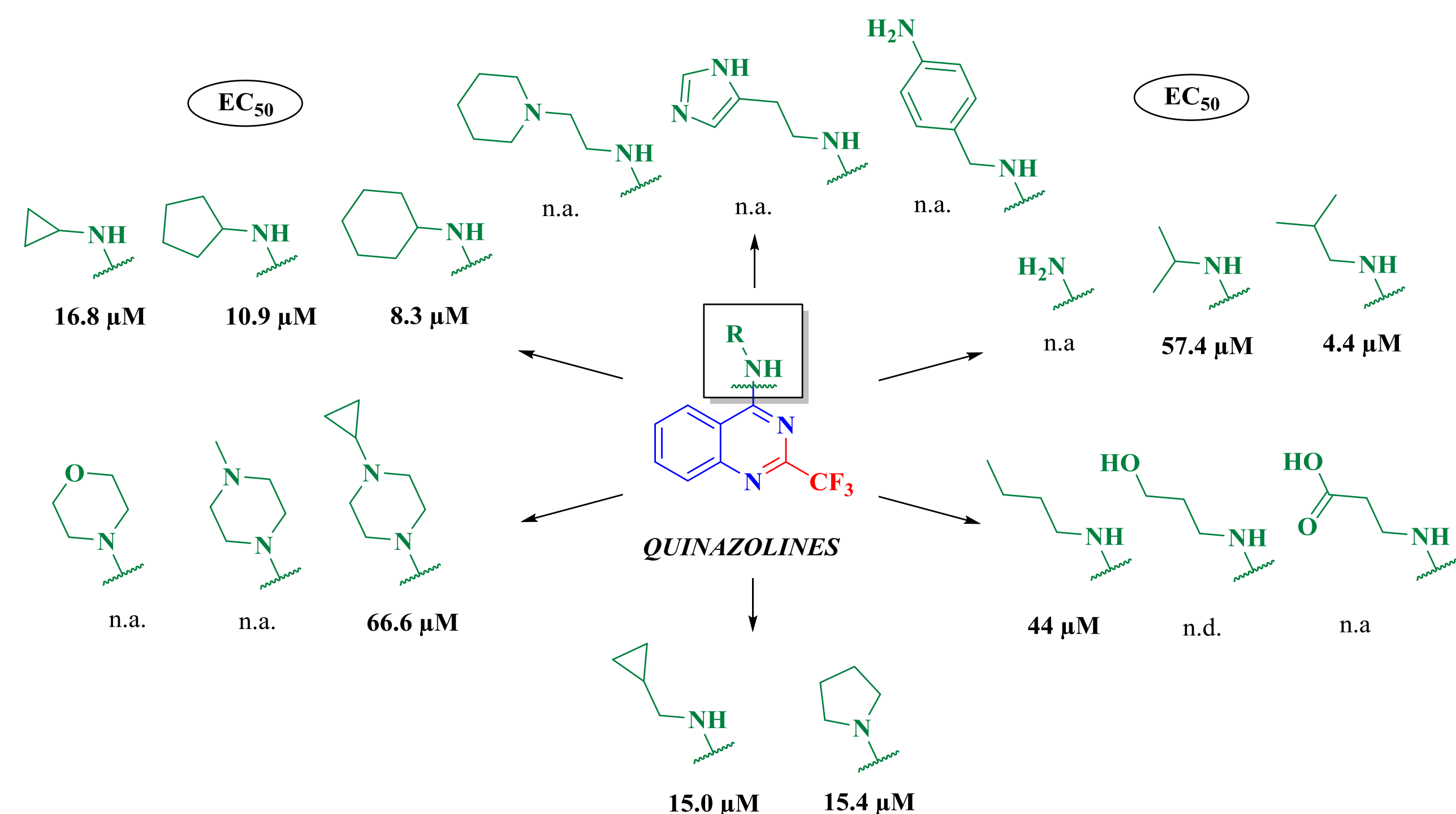
- used only locally on the skin
- unfavorable pharmacokinetic properties (induce strong local and systemic inflammatory reactions)

Imiquimod **the need for novel small molecule TLR modulators!**



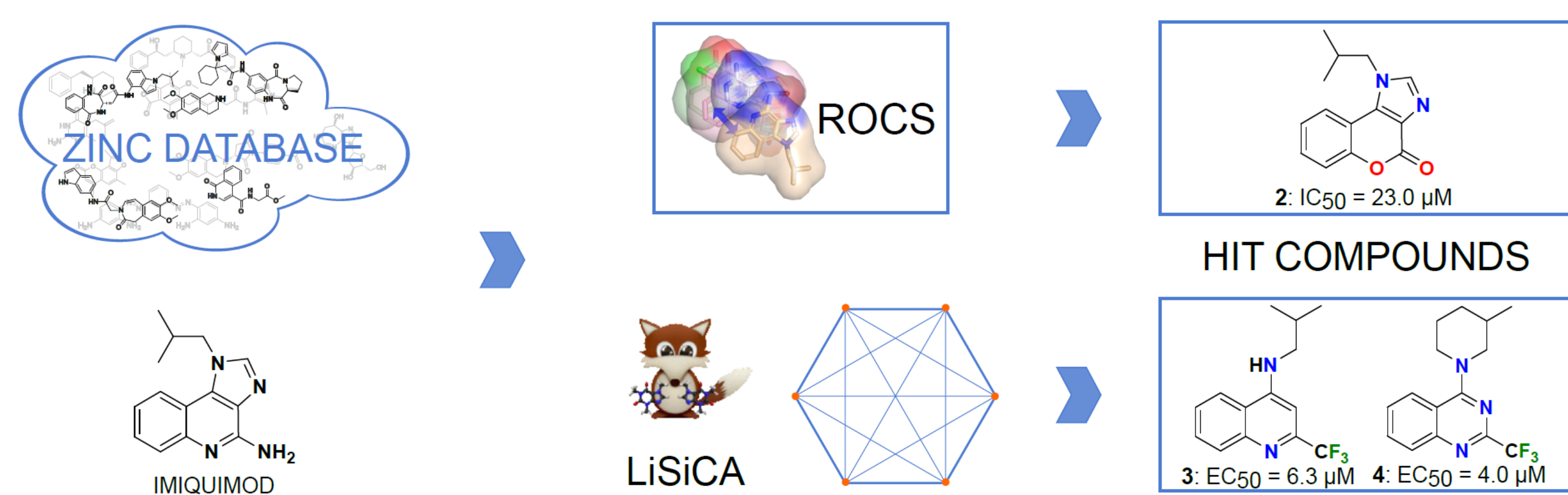
RESULTS

QUINAZOLINE series



IN SILICO DESIGN

Ligand-based virtual screening (ROCS, LiSiCA)

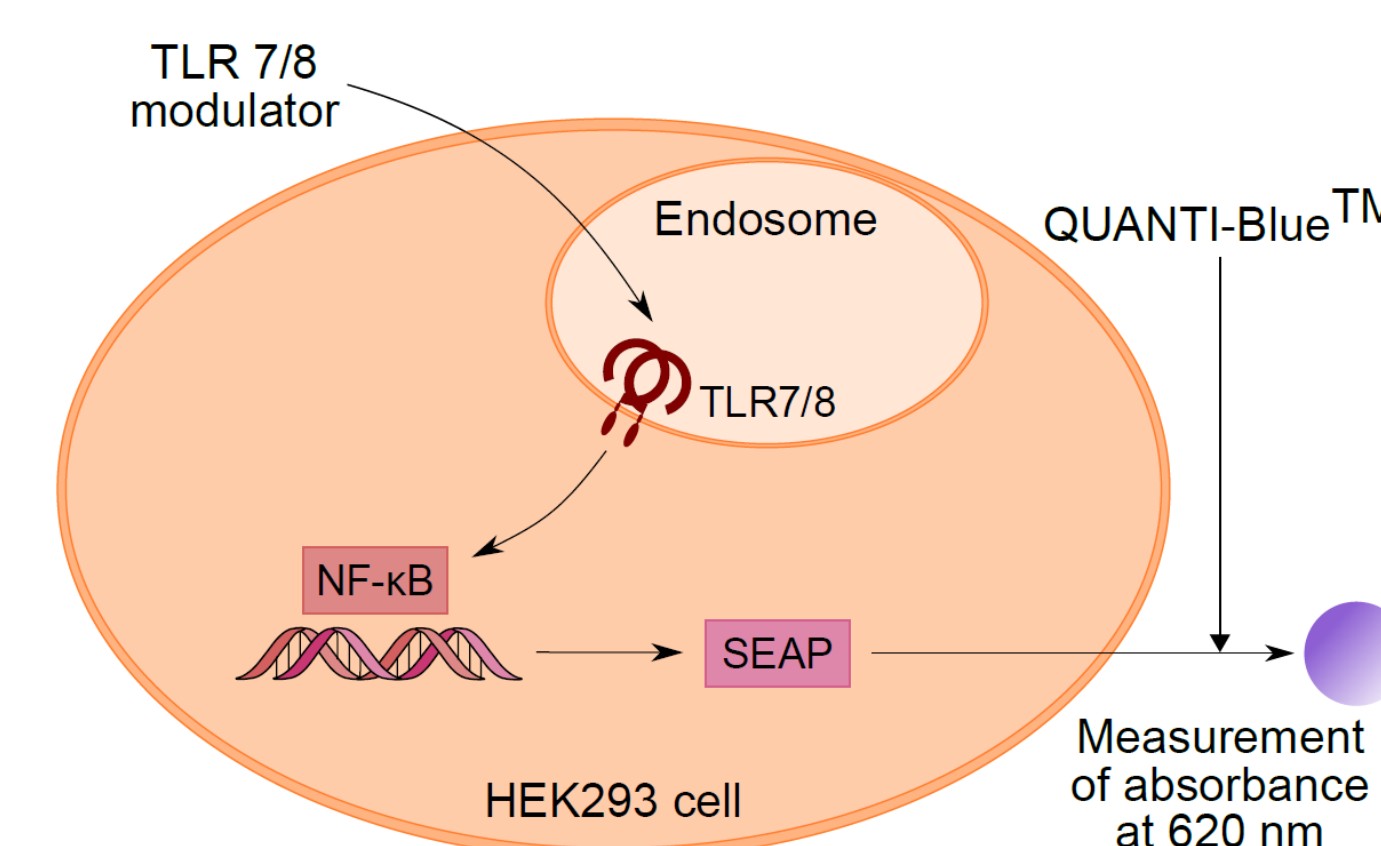
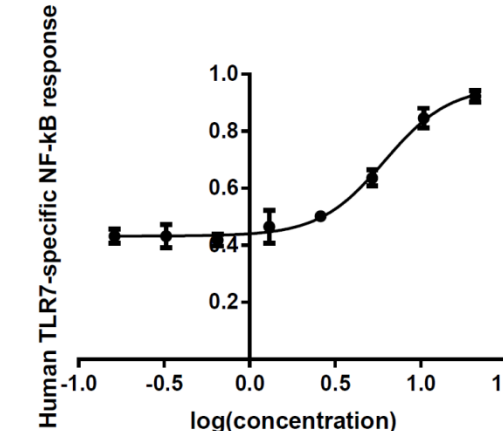
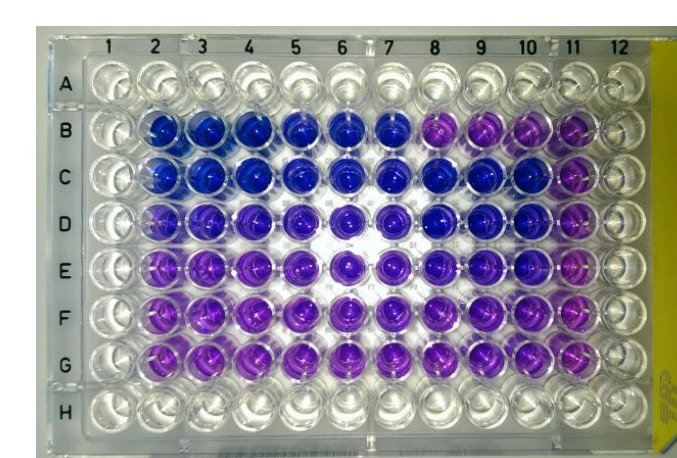


BIOLOGICAL EVALUATION

- TLR7 and TLR8 agonist activity evaluation

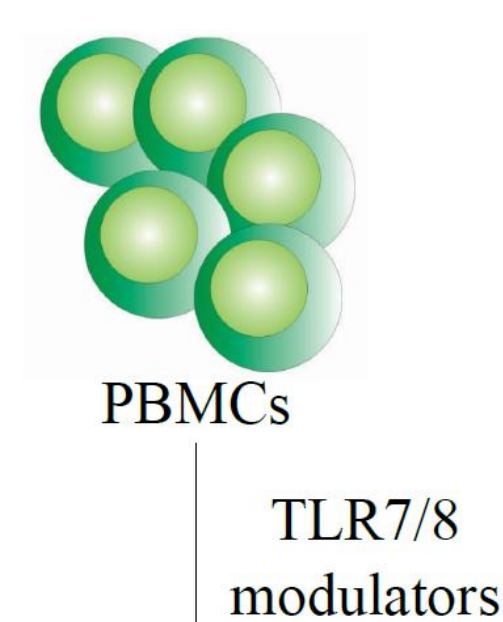
- HEK293 cell line, co-transfected with hTLR7 or hTLR8 gene and an inducible SEAP reporter gene

- EC₅₀ determination

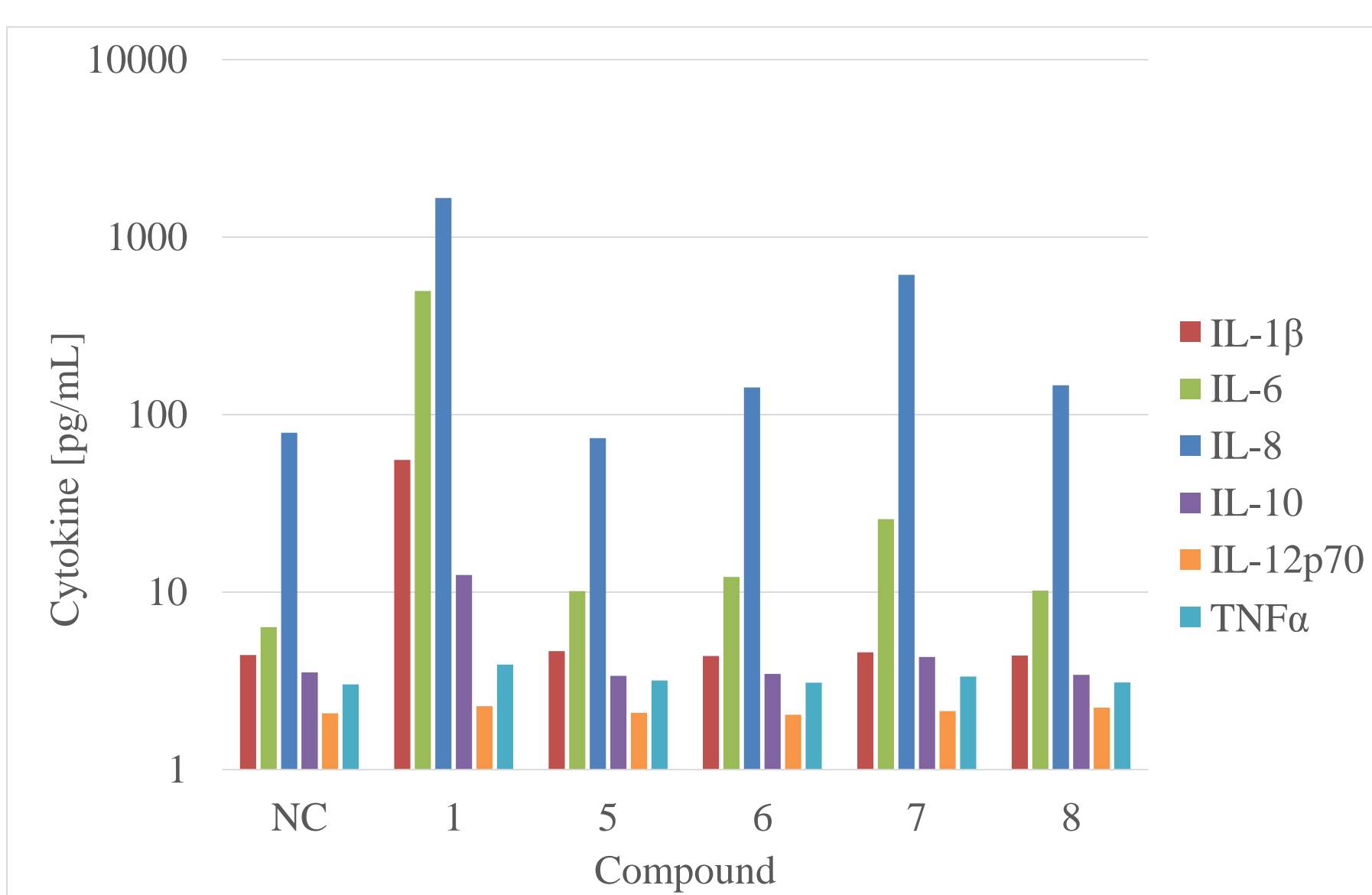


RESULTS: selective agonist activity on TLR7

CYTOKINE SECRETION ASSAY

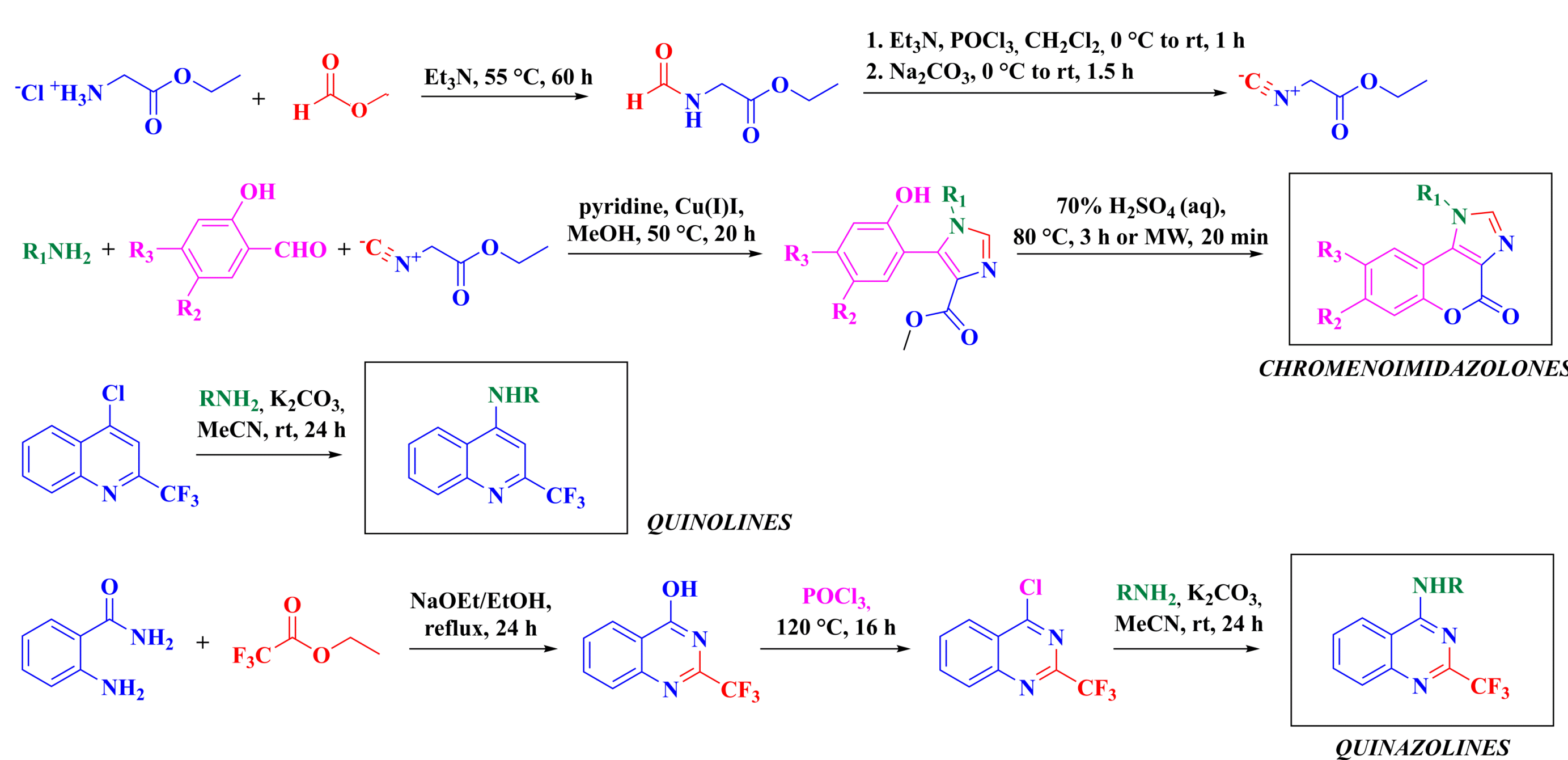


Cytokine secretion assay
IL-1β, IL-6, IL-8,
IL-10, IL-12p70, TNFα



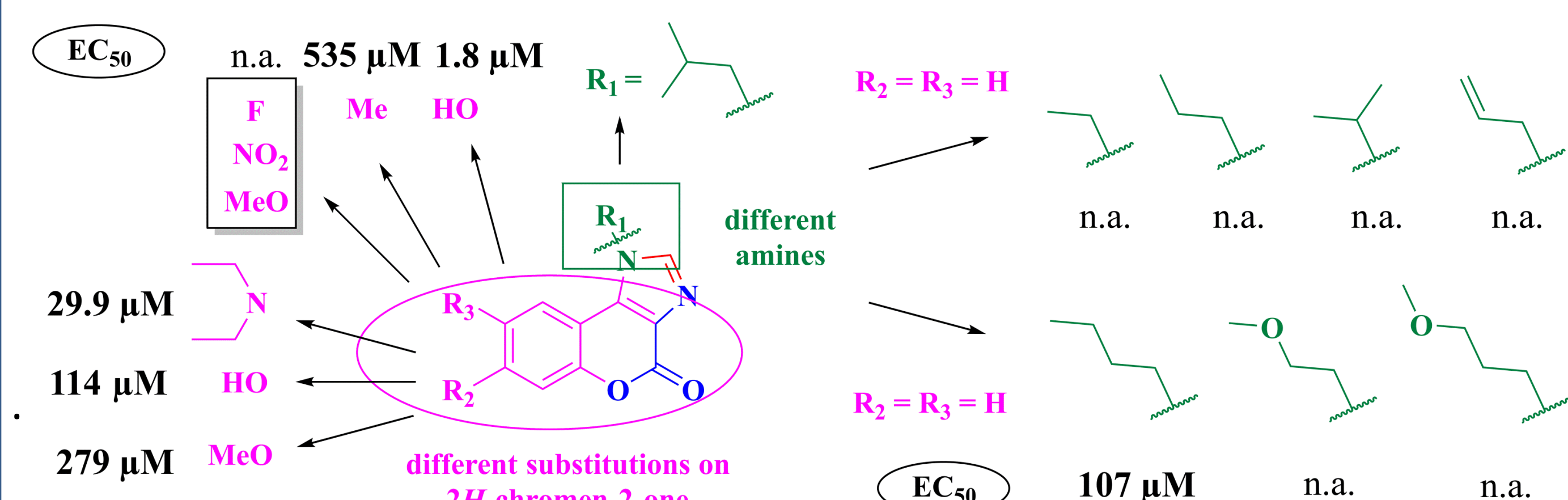
SYNTHESIS

Three scaffolds – development and optimization of synthetic procedures

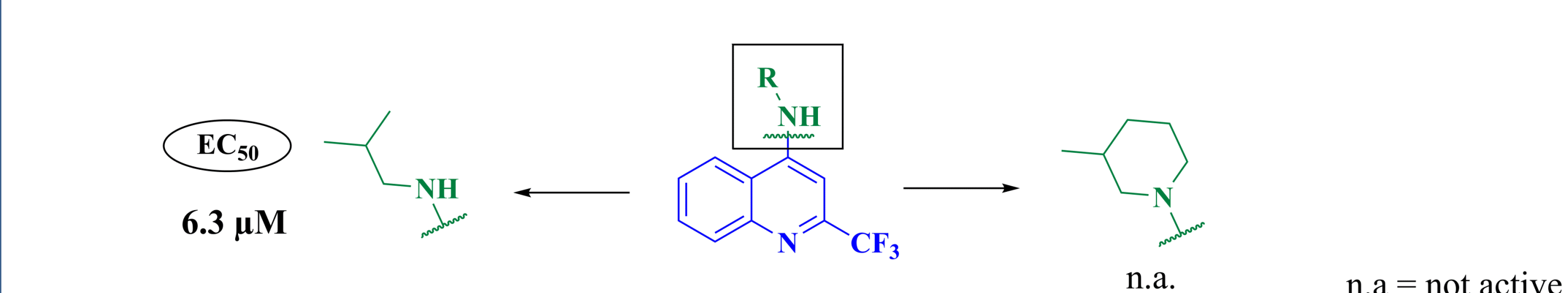


RESULTS

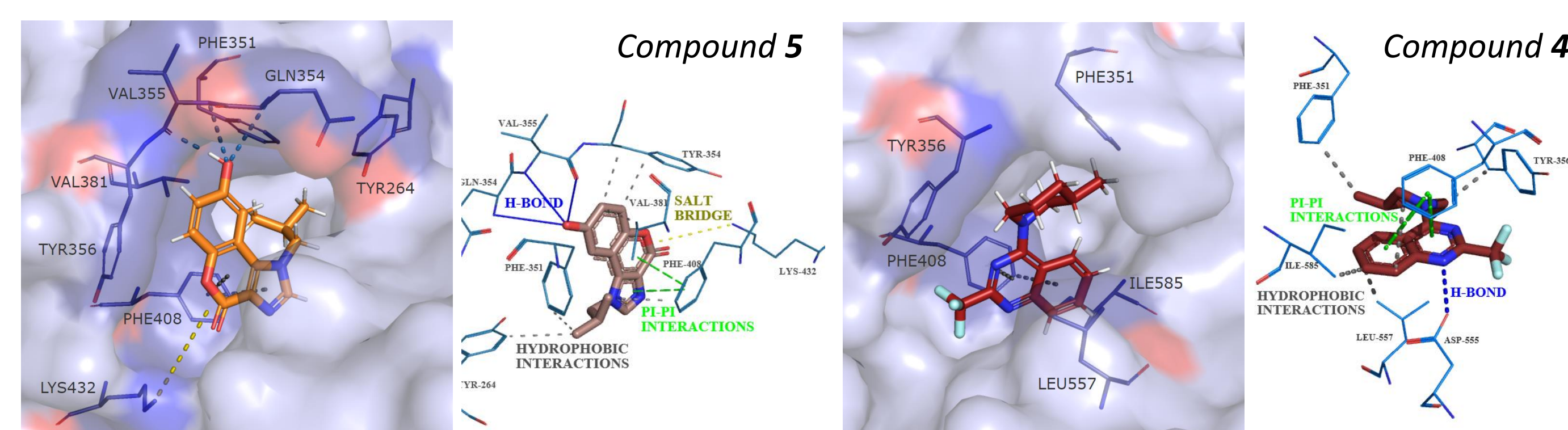
CHROMENOIMIDAZOLONE series



QUINOLINES



MOLECULAR DOCKING STUDY



Reference: Dolšak, A. et al., *Eur J Med Chem*, 2019, 18; 179: 109-122

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