Dynamic Cross-Correlation Matrix (DCCM) Reveals New Insights to Discover New NLRP3 Inhibitors Useful as Anti-inflammatory Drugs

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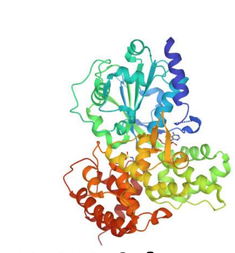
INTRODUCTION

The innate immune system is responsible for the body's defense against aggressive agents, mainly through activating pattern-recognition receptors (PRRs). Recognizing these agents results in an inflammatory response that activates tissue repair and eliminating the agent. Among the macromolecules related to these events are inflammasomes (inflammatory response activators), with emphasis on nucleotide-binding domain leucine-rich repeat-containing receptors protein 3 (NLRP3), in which blocking their oligomerization inhibits inflammasome activity. In this way, targeting NLRP3 represents a new approach to designing anti-inflammatory drugs. Here, molecular docking and dynamics, focusing on Dynamic Cross-Correlation Matrix (DCCM) analysis, were used to characterize significant interactions of MCC950 (known inhibitors) and their analog NP3-166 (ligand co-crystalized) with NLRP3 and generate useful information in drug design

EXPERIMENTAL SECTION



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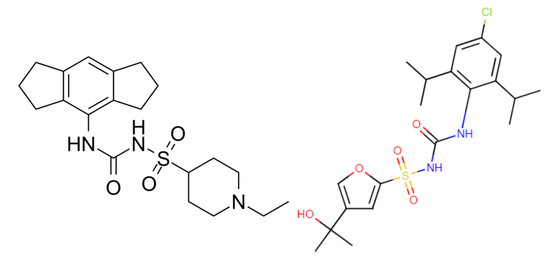
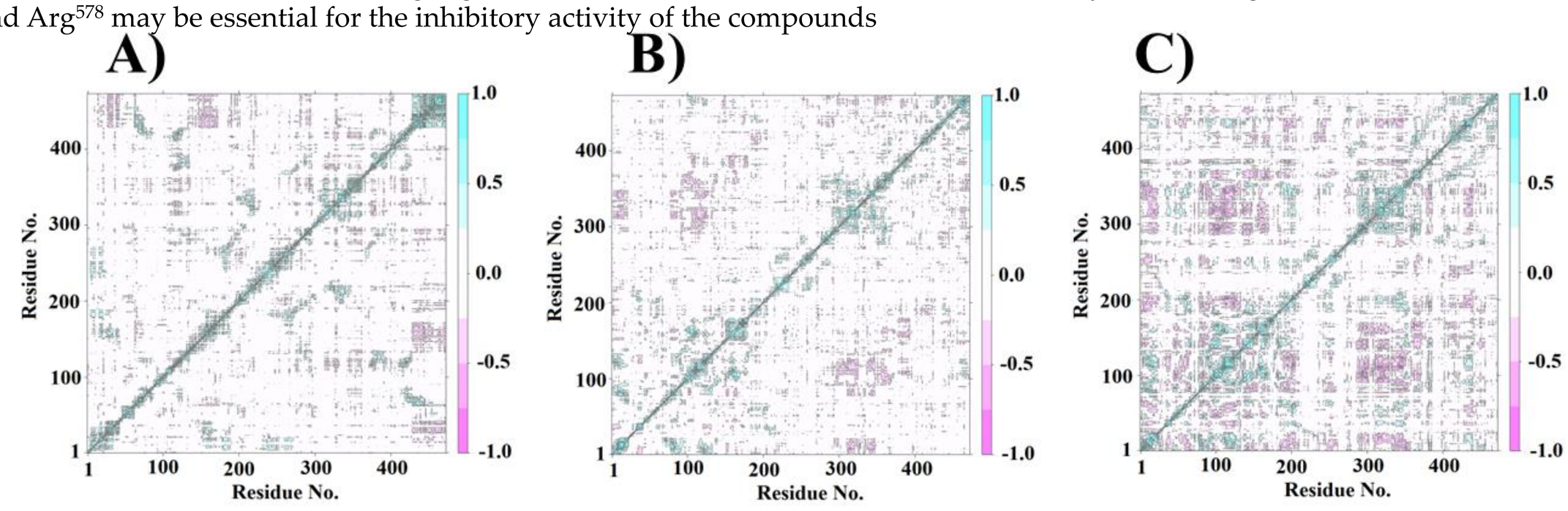


MCC950 and NP3-166

Docking *Dynamics (100 ns)* *DCCM*

RESULTS AND DISCUSSIONS

More correlated movements are presented for MCC950 **(C)** compared to NP3-166 **(B)** and free NLRP3 **(A)**. In fact, the more rigid structure of MCC950 may influence the more significant interaction. A higher correlation observed in both complexes between residues 100 – 200 and 300 – 400 highlights the results obtained from the interaction analysis, showing that interaction with Ala^{228} and Arg^{578} may be essential for the inhibitory activity of the compounds



CONCLUSION

Our findings highlight that greater structural rigidity of the ligand and interactions with residues Ala^{228} and Arg^{578} may be critical for designing new NLRP3 inhibitors with anti-inflammatory potential

REFERENCES

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