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Exploring Drug Repurposing for COVID-19: Investigating aclidinium's potential Effects on α7nAChR

*Ramon M. Cogo (PG)[1], Osvaldo Santos-Filho (PQ)[2], Carla M. Prado(PQ)[3], Daniela G. G. Rando (PQ)[1]**

•*ramon.cogo@unifesp.br; dgrando@unifesp.br*

• *1 Programa de Pós-Graduação em Biologia Química, Instituto de Ciências Ambientais, Químicas e Biológicas, Universidade Federal de São Paulo, campus Diadema– UNIFESP*

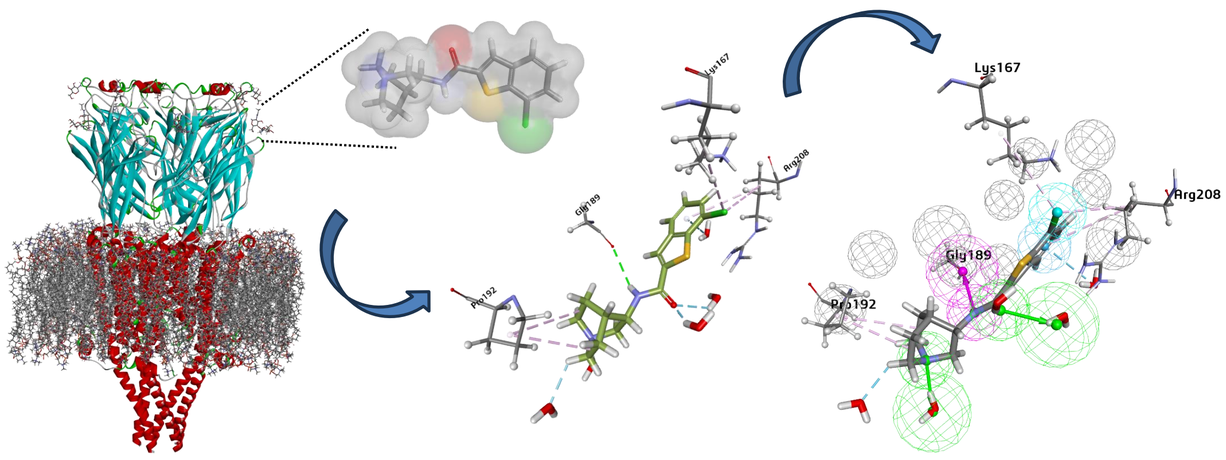
• *2 Laboratório de Modelagem Molecular e Biologia Estrutural Computacional, Universidade Federal do Rio de Janeiro, Rio de Janeiro – UFRJ*

•*3 Programa Interdisciplinar em Ciências da Saúde da Universidade Federal de São Paulo, campus Baixada Santista– UNIFESP*

•*Keywords: α7nAChR, anti-inflammatory cholinergic pathway, drug repurposing, molecular modeling, Sars-CoV-2.*

INTRODUCTION & AIMS

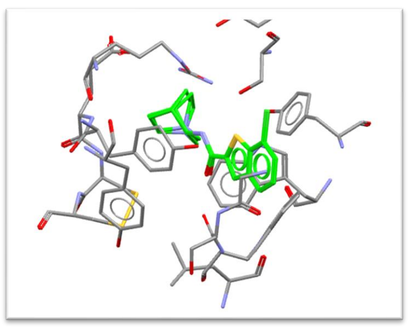
COVID-19 has led to over 7 million deaths globally. The virus interacts with ACE2 receptors, and as the disease progresses, it can trigger a cytokine storm, an intense inflammatory response associated with increased mortality. Since **α7nAChR** may modulate anti-inflammatory responses, this study investigates its agonists, their interactions, and employs pharmacophore modeling for virtual screening of FDA-approved drugs.

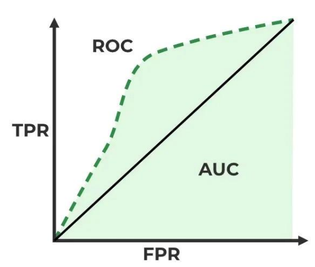


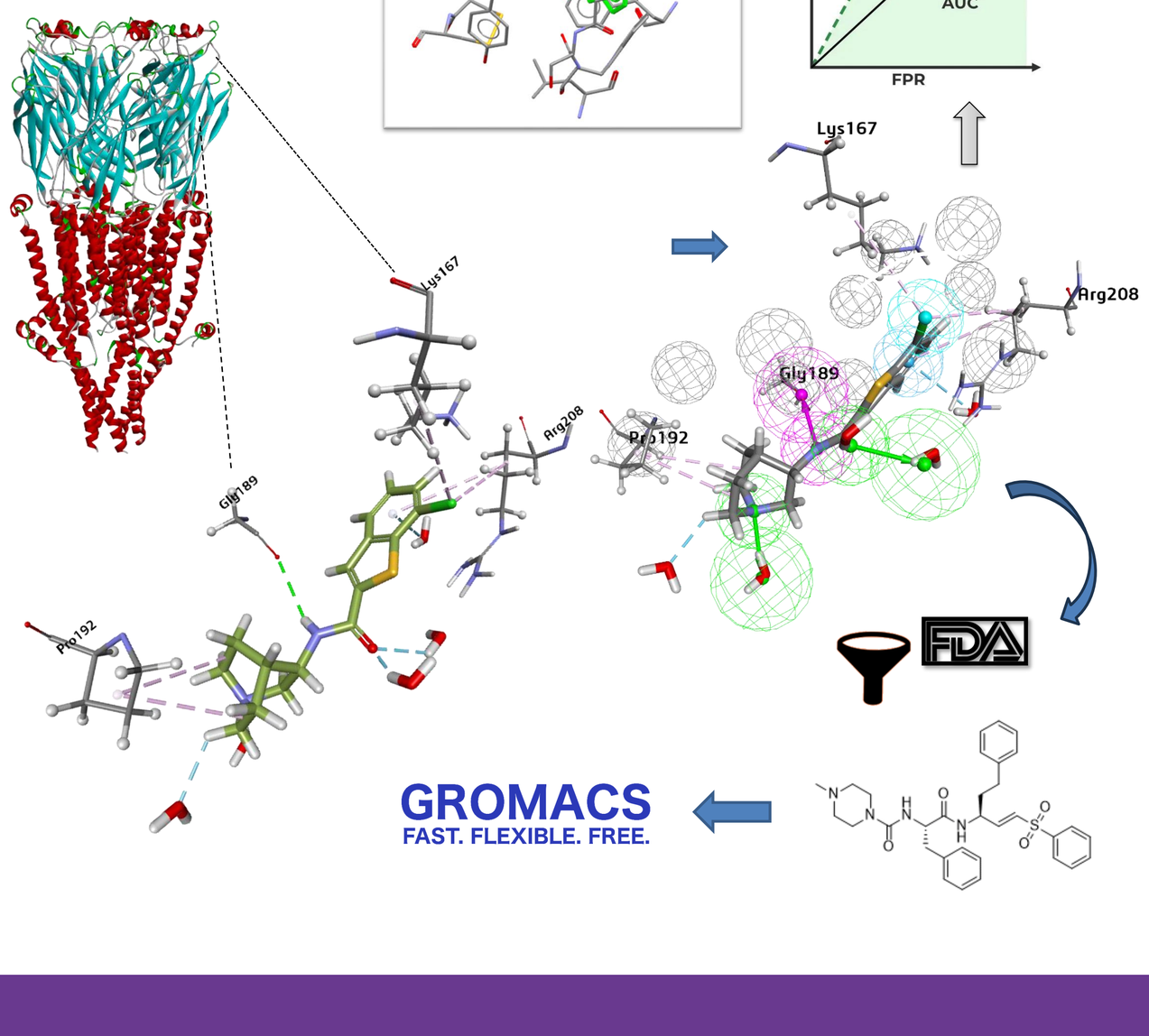
METHODS

Initially, EVP-6124 was redocked into the 7EKP structure using GOLD to establish the docking protocol. Subsequently, the 7EKI model underwent a 100 ns molecular dynamics (MD) simulation, followed by cluster analysis to identify the most representative conformation for docking EVP-6124. The best docking pose was then subjected to a 500 ns MD simulation until convergence was achieved. Pharmacophore models derived from representative conformations were validated through ROC curve analysis in BIOVIA Discovery Studio, yielding scores above 0.8. These validated models were subsequently employed to screen FDA-approved compounds. The virtual Screening results were docked using GOLD and evaluated with the GoldScore, ChemScore, ChemPLP, and ASP scoring functions. For each scoring function, 100 poses were generated and clustered within a 2 Å threshold. Representative clusters were then rescored using GNINA, and the top-scoring pose was selected for MD simulation.

7EKP – REDOCKING PROTOCOL
7EKI -> 100 ns MD
DOCKING (91% similarity)





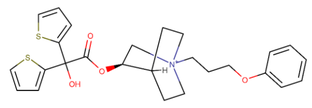


RESULTS & DISCUSSION

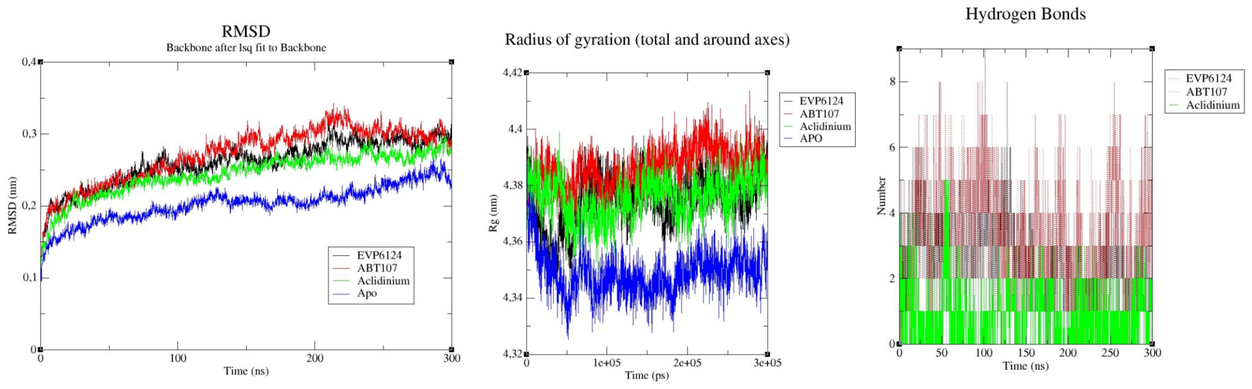
This method identified aclidinium (ACL) as a potential ligand for α7nAChR. ACL maintained stable interactions with the receptor for up to 300 ns. MD simulations of the partial agonist EVP-6124 and the full agonist ABT-107 were performed for comparison. All systems remained stable, as indicated by RMDS and radius of gyration analyses. Although ACL formed approximately half the number of hydrogen bonds, three key interactions were observed in the final MD frame, involving residues Tyr210, Cys212, and Trp77, with most hydrogen bonds mediated by water molecules. Functionally, both ACL and EVP-6124 target acetylcholine receptors, whereas structurally ACL more closely resembles EVP-6124 while retaining the conformational flexibility characteristic of antimuscarinic ligands.

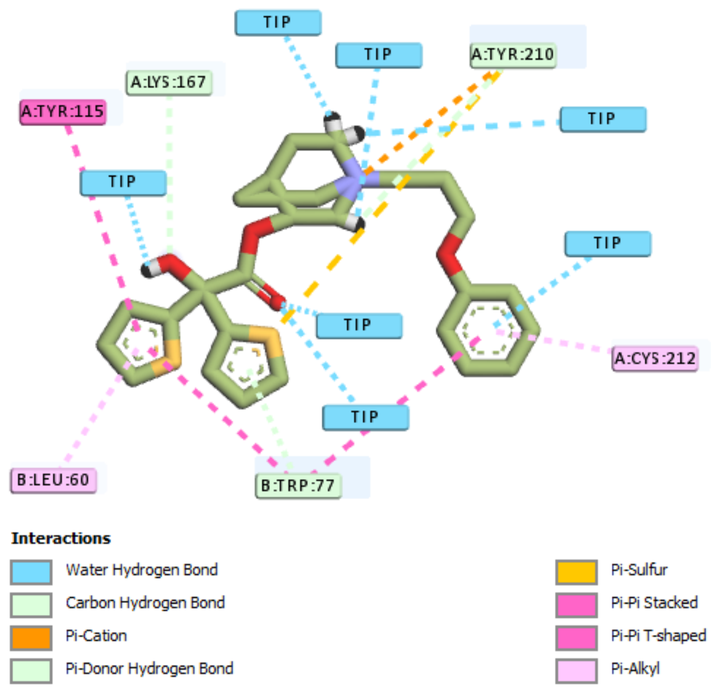
Farmacóforo	Total de ativos	Total de Inativos	Verdadeiros Positivos	Verdadeiros Negativos	Falsos Positivos	Falsos negativos	Sensibilidade	Especificidade	AUC ROC
01	123	305	103	241	64	20	0,83740	0,79016	0,799
02	123	305	103	239	66	20	0,83740	0,78361	0,799
03	123	305	101	206	99	22	0,82114	0,67541	0,722
04	123	305	98	222	83	25	0,79675	0,72787	0,737
05	123	305	101	207	98	22	0,82114	0,67869	0,714
06	123	305	101	222	83	22	0,82114	0,72787	0,737
07	123	305	114	208	97	9	0,92683	0,68197	0,805
08	123	305	113	104	201	10	0,91870	0,34098	0,814
09	123	305	114	206	99	9	0,92683	0,67541	0,804
10	123	305	113	105	200	10	0,91870	0,34426	0,786

BIOVIA
SBVS

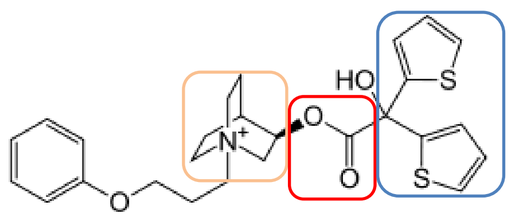


Aclidinium

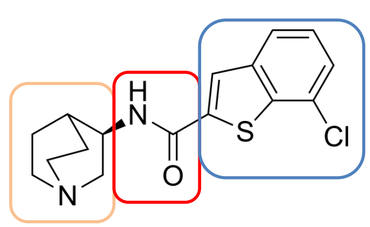




Antimuscarinic M3



α7 agonist



CONCLUSION

Aclidinium was highlighted as a potential ligand for α7nAChR, maintaining stable receptor interactions for up to 300 ns, and exhibiting structural similarity to EVP-6124.

FUTURE WORK / REFERENCES

- Estimate the free energy of binding through MM/PBSA
- Evaluate channel activation through CHAP pore analysis
- Conduct in vitro assays to evaluate compound behavior

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