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ANTIFUNGAL ACTIVITY, MOLECULAR DOCKING ON COVID-19 MAIN PROTEASE AND PHARMACOKINETICS OFIMIDAZOLONE ANALOGUES

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ABSTRACT

Eleven active imidazolone compounds were screened against two fungal species *Candida albicans* and *Fusariumricini* by MIC assay and*Griseofulvin* as standard reference. Insilico studies performed on SARs Cov2 main protease (M^{Pro}). The p-bromo, m-nitro, p-chloro, p-dimethyl amine substituted analogues exhibited outstanding MIC against both fungal strains compared to *Griseofulvin*. Molecular docking studies on these compounds unravel the relative orientation, mode of interaction and nature of bonding with proteinase of Candida albicans and SARs Cov2 main protease. The m,p-dimethoxy substituted analogue scored highest binding affinity against M^{pro}.The docking scores of all compounds are ranging between −8.70 to −11.07 Kcal/mol against the candida albicans proteinase and -8.77 to -12.01 Kcal/mol against SARs Cov2 main protease. The pharmacokinetics evaluation performed by using SwissADME web server identified their more drug-likeness properties.

KEYWORDS: Imidazolones,antifungal activity, autodock, COVID-19, molecular docking

INTRODUCTION

Rendering to the literature evaluation, heterocyclic compounds epitomize imperativerole in medicinal chemistry[i].Abundant imidazole-based clinical drugs play imperious position in handling arange of diseases[ii]. Novel imidazoleswith curative values are being aggressively exploited worldwide[iii]. Imidazoles exist in tautomeric forms and bind with receptors through vanderwaalsforces, hydrogen bonding, dipole-dipole and π bonding interactionsthereby exhibiting broad biological activities[iv].Imidazolones are classified based on the position of carbonyl group as2-oxo-imidazoline, 4-oxoimidazoline and 5-oxoimidazoline[v].These are structurally correlated to amidines as well as guanidines.A diverse range of imidazolone-5-ones holda widespread band of biological and pharmacological actions which are unveiled by their use as CNS depressant[vi], antifungal[vii],antihelmentic[viii], anticancer[ix], anticonvulsant and monoaminoxidase inhibition[x,xi] and antiparkinsonian[xii].

Molecular docking is a computational procedure that aims to predict the favored orientation of a ligand to its macromolecular target (receptor) when these are bound to each other to form a stable complex[xiii]. It is a reliable, cost-effective, and time-saving technique in

the process of drug discovery[xiv]. Various docking tools are available for academic and commercial purpose, such as DOCK[xv], Autodock[xvi], AutodockVina[xvii], PyRx[xviii], Glide[xix], GOLD[xx] etc.

Inspired by potent biological activities of imidazolones, extension of our previous work reported[xxi], we further investigated the antifungal activity and *insilico* screening on SARs-Cov2 main protease.

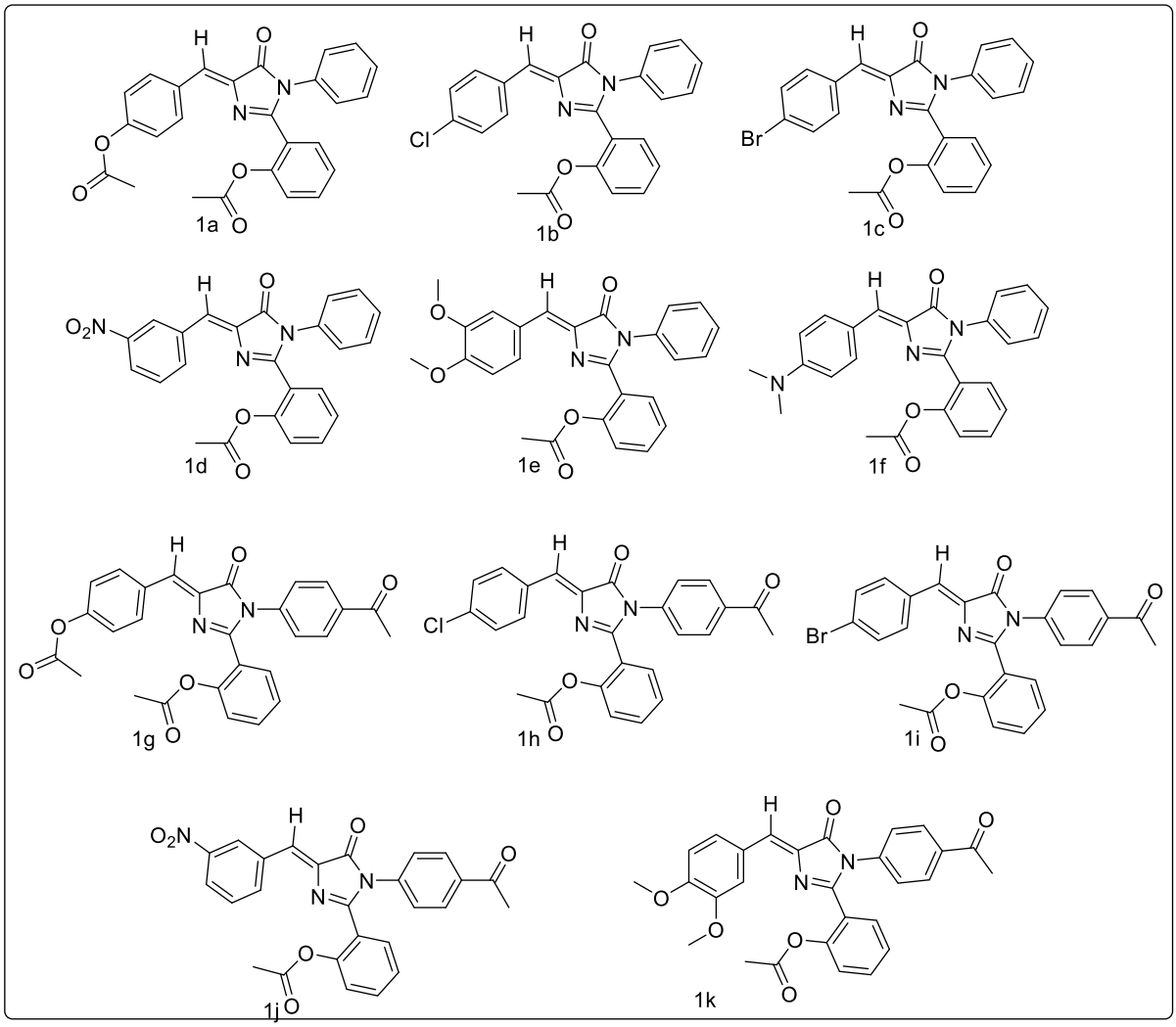

Fig 1. Structures of Imidazolone analogues**1a-k**

RESULTS AND DISCUSSION

Antifungal Activity

All eleven imidazolone analogues werescreened against two fungal strains viz. *Fusarium ricini* and *Candida albicans*. The minimum inhibitory concentration (MIC) results of all compounds are presented in **Table-1.** The compounds **1c, 1d, 1h, 1f, 1j** and **1k** exhibited good inhibition against the *F.ricini* compared to *Griseofulvin*. Similarly, compounds **1d, 1e, 1f, 1g, 1h, 1i** and **1k**executed superior activity against *C.albicans* than standard*Griseofulvin*. It may be attributed to the presence of electron withdrawing nature of acetyl, chloro, bromo, nitro, methoxy group substitution by inductive effect and electron donating nature of dimethyl amine group substitution.The activity of compounds are shown in Fig **1 & 2**.

Table 1: The minimum inhibitory concentration results of imidazolone compounds

Sample	Growth Inhibition of Fungal Organism (mm)	
	Fusarium ricini	*Candida albicans*
1a	15mm	20mm
1b	16mm	20mm
1c	18mm	20mm
1d	18mm	25mm
1e	16mm	25mm
1f	16mm	25mm
1g	16mm	25mm
1h	18mm	25mm
1i	18mm	25mm
1j	18mm	18mm
1k	18mm	25mm
standard	15mm	18mm
control	25mm	30mm

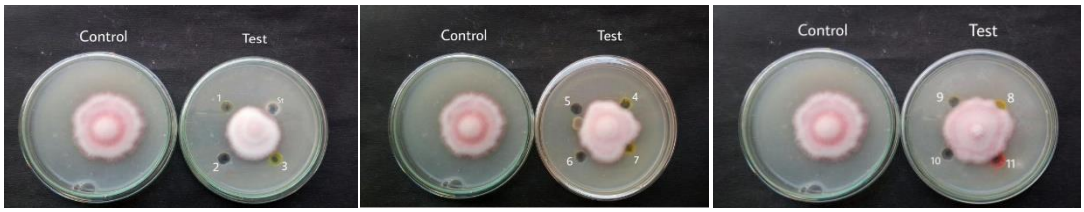

Fig 2. The antifungal activity of imidazolone compounds against *Fusarium ricini*

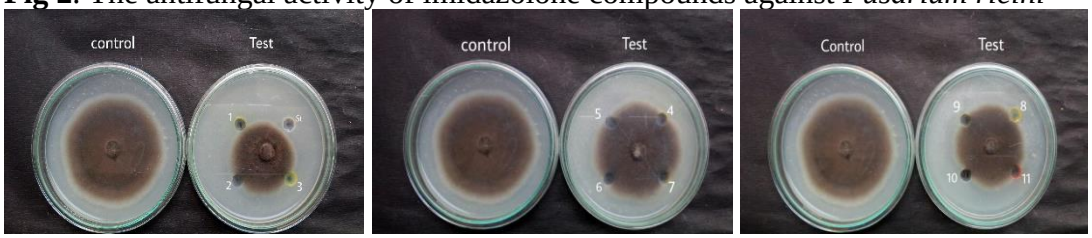

Fig 3. The antifungal activity of imidazolone compounds against *Candida albicans*

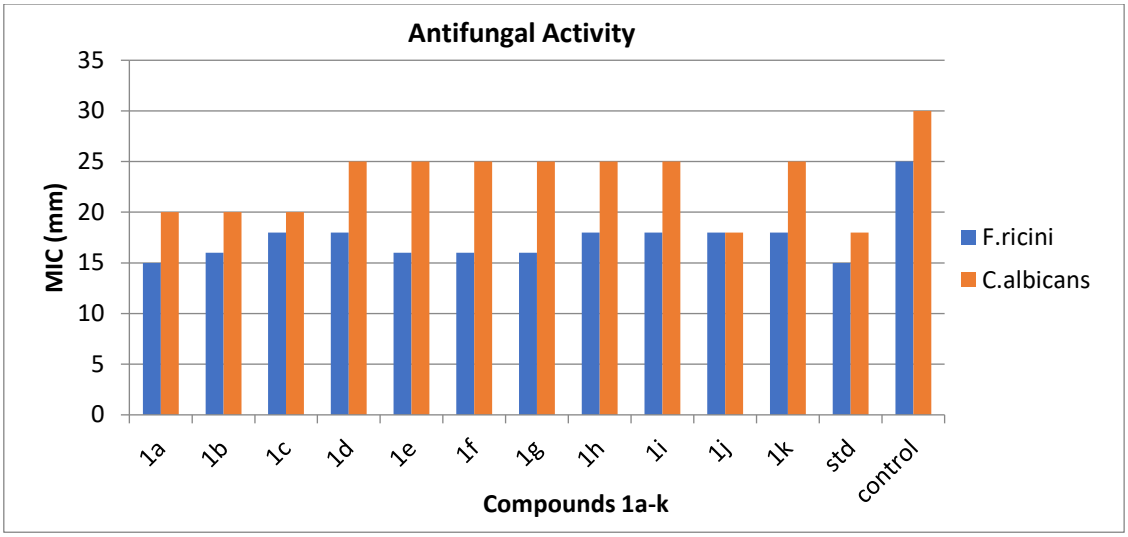

Fig 4. Graph representing MIC values of imidazolone compounds**1a-k**

Molecular docking against of aspartic proteinase

Docking simulation were performed on crystal structure of aspartic proteinase (PDB ID: 2QZW) [xxii] of *Candida albicans*.The binding affinity values by all molecules were found to be outstanding than*Griseofulvin*, except for compound **1c**. The docking score and binding interactions of compounds **1a-k** are presented in table-2.

Table 2: Docking scores of compounds 1a-k and binding interactions with aspartic proteinase

Compound	Binding Affinity (Kcal/mol)	Interacting Amino acids	
		H-bonds	Hydrophobic bond
1a	-9.3	Asp32, Arg192, Thr221, Ser336	Ile30, Tyr84, Asp86, Ile123
1b	-5.73	Gly85, Asn160	Gly87, Gln168, Lys178, Ser334, Ile338
1c	-8.7	Gly85, Gly220	Ile123, Ile305, Ala335
1d	-8.93	Ser336	Tyr84, Tyr225, Ala303, Ile305
1e	-8.43	Gly85, Ser336	Gly34, Tyr84, Ile123, Ile305
1f	-8.96	Asp86	Tyr84, Gly85, Asp86, Ile305, Asn337
1g	-10.56	Ile223, Tyr225, Ser301	Gly85, Ser301, Ile305
1h	-10.6	Asp32, Arg192, Thr221	Gly85, Ile123, Ile305
1i	-9.49	Asn131	Tyr84, Gly85, Ala303, Ile305, Ala335, Asn337
1j	-8.99	Gly85, Arg192	Tyr84, Leu216, Thr221
1k	-8.91	Asp32, Gly85, Asn131, Asp218, Thr222	Tyr84, Asp86, Leu216
Griseofulvin	-6.00	Ser88	Ser13, Ile30, Asp86, Ile119, Pro120, Ile123, Gly220, Thr221

Compound **1h,** 4-chloro substituted analogue scored highest binding affinity value about -10.6 Kcal/mol. It demonstrated key interactions with Asp32, Arg192, Thr221 and hydrophobic interactions with Gly85, Ile123, Ile305 of aspartic proteinase (**Fig 5, 6**). The standard drug *Griseofulvin* scored just -6.00 Kcal/mol binding energy value and it indicated only one H-bond interaction with Ser88 of 2QZW (**Fig 7, 8**). The binding energies and interactions of all compounds (**1a-k**) with aspartic proteinase (PDB ID: 2QZW) proved that all compound best fit into theactive site pocket and can show inhibition.

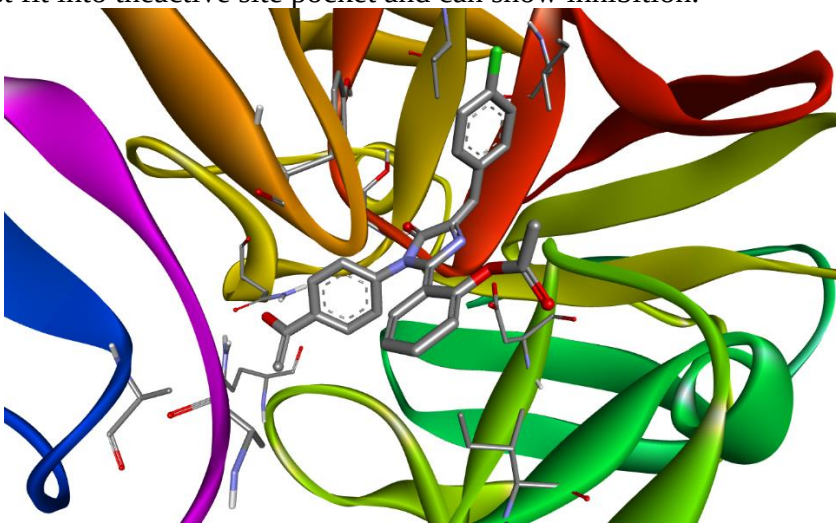

Fig 5. Docking pose of compound **1h** in cavity of aspartic proteinase (PDB ID: 2QZW)

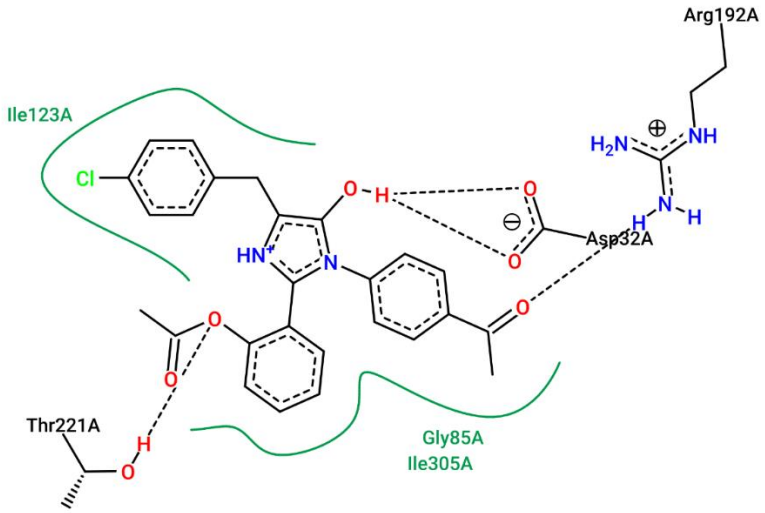

Fig 6. 2D interactions of compound **1h** with aspartic proteinase (PDB ID: 2QZW)

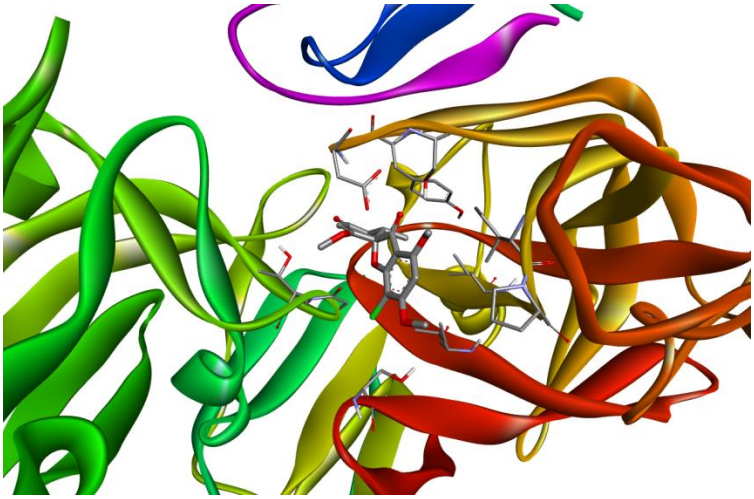

Fig 7. Docking pose of griseofulvin in cavity of aspartic proteinase (PDB ID: 2QZW)

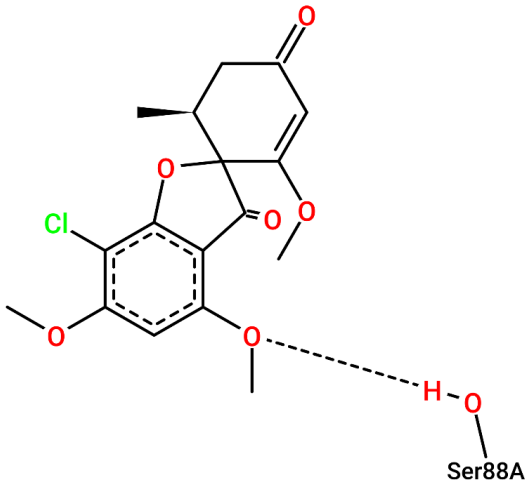

Fig 8. 2D interactions of griseofulvin with aspartic proteinase (PDB ID: 2QZW)

MOLECULAR DOCKING WITH COVID-19 MAIN PROTEASE

With an interest to study the inhibition of SARs corona virus, molecular docking studies performed on COVID-19 main protease (PDB ID: 6LU7) [xxiii]-[xxv](M^{Pro}) of corona virus. The active site pocket of 6LU7 is occupied with amino acids His41, Met49, Tyr54, Phe140, Leu141, Asn142, Gly143, His163, Met165, Glu166, Leu167, His172,Phe185, Asp187, Gln189 and Gln192[xxvi]. The binding energies of all compounds **1(a-k)** were ranging from -8.77 to -10.68 Kcal/mol as shown in Table-3.

Table-3: Docking sores and binding interactions of compounds **1(a-k)** against COVID-19 main protease

Compound	Binding Affinity (Kcal/mol)	Interacting Amino acids	
		H-bonds	Hydrophobic bond
1a	-10.13	His41, Gly143, Cys145	Cys145, Met165, Arg188, Gln189
1b	-9.14	His163, Arg188	His41, Cys145, Asp187, Gln189
1c	-8.92	His163, Arg188	His41, Cys145, Asp187, Gln189

1d	-10.23	His41, Glu166	His41, Met49, Cys145, Met165, Asp187, Arg188, Gln189
1e	-9.64	Gly143, Glu166	His41, His163, Met165, Glu166, Arg188, Gln189
1f	-9.4	-	-
1g	-9.72	His41, Gly143, Cys145	Cys145, Met165, Arg188, Gln189
1h	-10.53	Gln192	Met165, Glu166, Gln189
1i	-10.68	Glu166, Arg188, Gln192	Met165, Arg188, Gln189
1j	-8.77	His41, Cys145, Glu166	His41, Met49, Met165, Asp187, Gln189
1k	-8.96	His163, glu166, Gln189	Met165, Gln189

Compound **1i**, 4-bromo substituted analogue possesses highest binding energy of -10.68 Kcal/mol. Interestingly, it indicated H-bond interactions with active site amino acids Glu166, Arg188, Gln192 and hydrophobic interactions with Met165, Arg188, Gln189 of M^{Pro} (**Fig 9, 10**). Compound **1h** scored second highest binding energy of -10.53 Kcal/mol, it demonstrated a H-bond interaction with Gln192 and hydrophobic interactions with Met165, Glu166, Gln189 of M^{pro}(**Fig 11, 12**). The binding energies and interactions of best confirmers indicate that these molecules could inhibit the corona virus and can be investigated experimentally in near future.

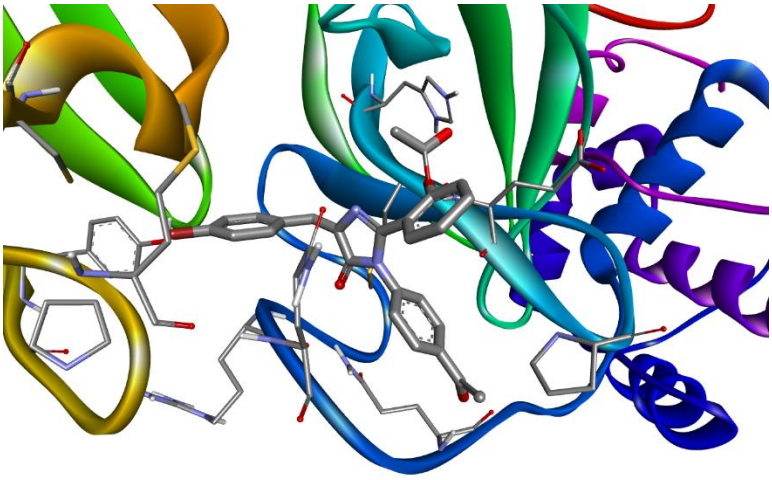

Fig 9. Docking pose of compound **1i** in cavity of M^{pro}

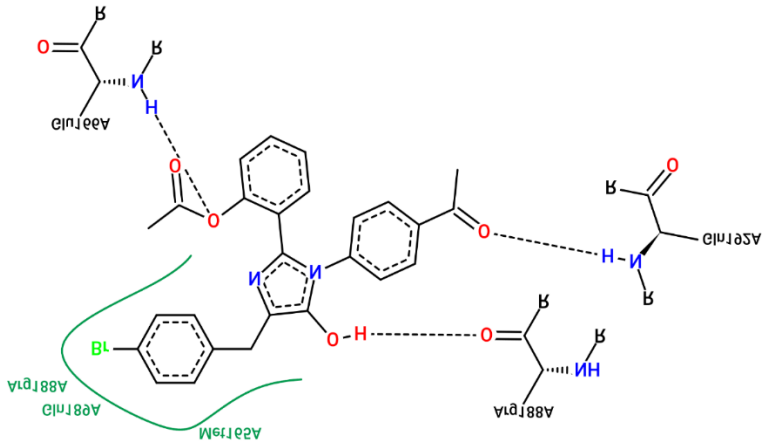

Fig 10. 2D interactions of compound 1i in cavity of M^{pro}

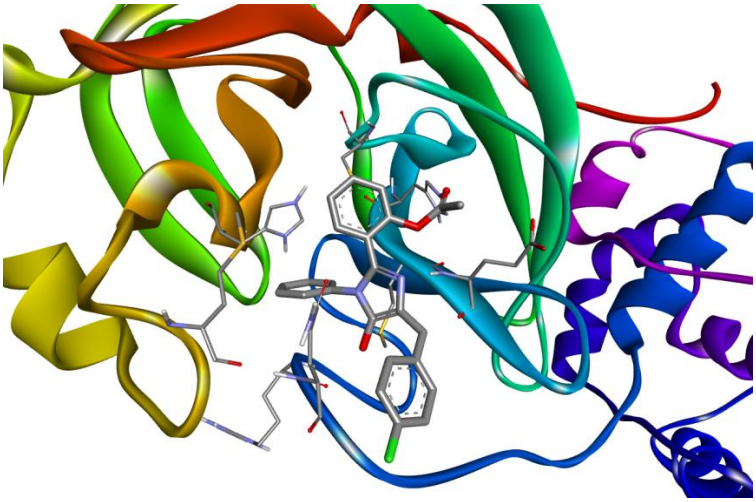

Fig11. Docking pose of compound**1h** in cavity of M^{pro}.

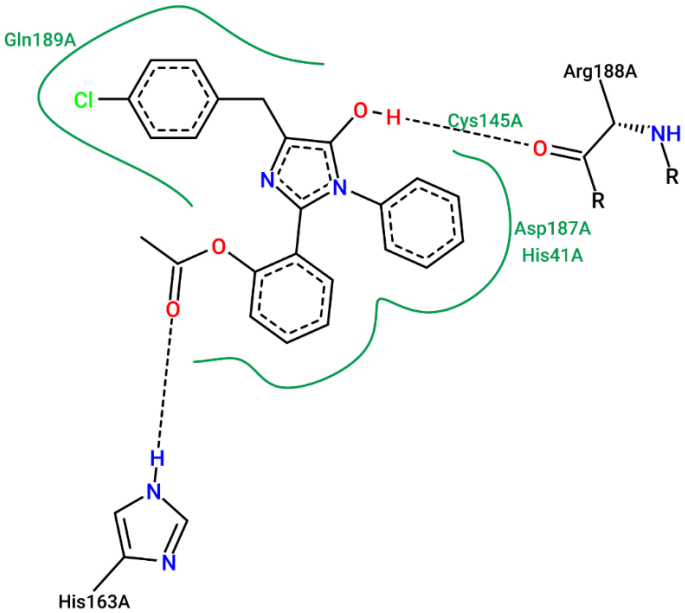

Fig 12. 2D interactions of compound 1h in cavity of M^{pro}.

PHARMACOKINETIC EVALUATION

Absorption, Distribution, Metabolism and Excretion properties are important in the process of drug discovery. The calculated pharmacokinetics of the studied compounds**1(a-k)** shown in **Table-4.** Except compound 1i,all the tested compoundshave molecular weight below 500 g/mol. The molecular weight characteristics of these molecules suggested that they can easily be transported, diffused, and absorbed in the body in a significant manner[xxvii]. The LogP value of the compounds were found to be in the range of 3.12–4.1, which meet the essential conditions of the Lipinski's rule of five[xxviii]. The calculated number of H-bond acceptors of all the molecules were less than ten which is in accordance with ADME as the number of hydrogen bond acceptors must be <10. Bioavailability score of 0.55 suggested that these molecules can be absorbed and used by body[xxix]. Synthetic accessibility scores recommended the ease of synthesis of these molecules[xxx].

Table-4: Drug-likeness properties of compounds **1a-k**

Compound	Molecular Weight	Rotatable bonds	H-bond acceptors	H-bond donors	Molar Refractivity	TPSA	iLOGP	ESOL Log S	GI absorption	Lipinski violations	Bioavailability Score	Synthetic Accessibility
1a	440.45	7	6	0	130.59	85.27	3.98	-5.18	High	0	0.55	3.85
1b	416.86	5	4	0	124.1	58.97	3.79	-5.76	High	1	0.55	3.61
1c	461.31	5	4	0	126.79	58.97	3.85	-6.07	High	1	0.55	3.65
1d	427.41	6	6	0	127.91	104.79	3.26	-5.23	High	0	0.55	3.78
1e	442.46	7	6	0	132.07	77.43	4.1	-5.31	High	0	0.55	3.96
1f	425.48	6	4	0	133.29	62.21	4	-5.4	High	0	0.55	3.92
1g	482.48	8	7	0	140.78	102.34	3.49	-5.14	High	0	0.55	3.98
1h	458.89	6	5	0	134.29	76.04	3.72	-5.71	High	0	0.55	3.74
1i	503.34	6	5	0	136.98	76.04	3.89	-6.02	High	2	0.17	3.77
1j	469.45	7	7	0	138.1	121.86	3.12	-5.18	High	0	0.55	3.9
1k	484.5	8	7	0	142.26	94.5	3.93	-5.28	High	0	0.55	4.09

MATERIALS AND METHODS

Antifungal Assay

The antifungal assay is performed by using two fungi,*Fusarium ricini* and *Candida albicans*. Potato dextrose agar plates were made and 5mm diameter fungal plugs were placed carefully at the center of the plate around which 5mm wells were made using sterile well borer based on number of samples[xxxi]. The wells were loaded with 100µl of samples each and one well with antifungal chemical as standard (*Griseofulvin***)**. The plates were incubated for 96 hours at 25°C and results were noted.

Molecular DockingStudy

The Autodock 4.2 is an open source software which was downloaded from The Scripps Research Institute (www.scripps.edu) into the computer configured with Intel(R) Core(TM) i5-8250U CPU @ 1.60GHz1.80 GHz processor and RAM capacity of 16.00GB. The ligand molecules were drawn using the tool ChemSketch (www.acdlabs.com) in .mol format and converted to PDB file using Pymol (pymol.org) program tool.

To study the binding interactions between the newly synthesized ligands and the target molecules, the Secreted aspartic proteinase from *Candida albicans* (PDB ID: 2QZW) and Covid-19 main protease (PDB ID: 6LU7) were downloaded from Protein Data Bank (www.rcsb.org). The ligands and the target proteins were loaded into Autodock 4.2, the number of torsions were set to the ligands. Both ligand and target proteins were saved into PDBQT format. The Grid box for 2QZW was set up with 60:60:60 A^0 and coordinates -16.302, -23.24 and -16.245 were assigned[xxxii]. The Grid box for 6LU7 was set up with 60:60:60 A^0 and coordinates -11.824, 14.735 and 74.152 were assigned[xxiv]. To obtain best docking results 10 confirmers of each ligand were run in Autodock 4.2.

The Autodock 4.2 uses a Lamarckian genetic algorithm program to calculate different ligand conformers. Conformations were ranked according to the binding energy obtained from docked procedure and the confirmation with lowest binding energy was considered as the best docking score. The Autodock 4.2 results were visualized by using BIOVIA Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download) and Proteins Plus Server (https://proteins.plus/).

Pharmacokinetics

SwissADME web server protocol was used to evaluate the drug-likeness properties of all compounds[xxxiii].

CONCLUSION

Invitro antifungal assay results confirm that compounds **1c, 1d, 1e, 1f, 1h, 1i, 1j** and **1k**demonstrated potent activity against two fungal strains viz. *Fusarium ricini* and *Candida albicans*. The docking studies on aspartic proteinase of candida albicans support the investigational data. Molecular docking on M^{pro} confirms that they bind in active site pocket with good binding affinities so that we can proceed for further experimental studies in mitigating the virus responsible for pandemic conditions across the world.

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DECLARATION

All authors declare that there is no conflict of interest

REFERENCES

i. J. Jampilek, "Heterocycles in Medicinal Chemistry.," *Molecules (Basel, Switzerland)*, vol. 24, no. 21. Oct. 2019. doi: 10.3390/molecules24213839.
ii. S. S. Alghamdi, R. S. Suliman, K. Almutairi, K. Kahtani, and D. Aljatli, "Imidazole as a Promising Medicinal Scaffold: Current Status and Future Direction.," *Drug Des. Devel. Ther.*, vol. 15, pp. 3289–3312, 2021, doi: 10.2147/DDDT.S307113.
iii. A. Bhatnagar, P. K. Sharma, and N. Kumar, "A review on 'imidazoles': Their chemistry and pharmacological potentials," *Int. J. PharmTech Res.*, vol. 3, pp. 268–282, Jan. 2011.
iv. S. Kubik and D. Mungalpara, "Amino Acid-Based Receptors," *Compr. Supramol. Chem. II*, vol. 3, pp. 293–310, Jun. 2017, doi: 10.1016/B978-0-12-409547-2.12528-4.
v. M. R. Grimmett, *Imidazole and benzimidazole synthesis*. Academic press, 1997.
vi. J. K. Gupta, B. De, and V. S. Saravanan, "Pharmacological evaluation of synthetic imidazolinones and their schiff bases," *Indian J. Pharm. Sci.*, vol. 67, no. 3, p. 373,

2005.

vii. K. M. Khan, U. R. Mughal, S. Khan, S. Khan, S. Perveen, and M. I. Choudhary, "Synthesis and antibacterial and antifungal activity of 5-substituted imidazolones," *Lett. Drug Des. Discov.*, vol. 6, no. 1, pp. 69–77, 2009.

viii. N. Kortiwala, J. Patel, and V. A. Desai, "Imidazolone and its various biological activities–a review," *J. Chem. Chem. Sci.*, vol. 6, no. 1, pp. 25–32, 2016.

ix. A. Kamal *et al.*, "Synthesis and anti-cancer activity of chalcone linked imidazolones," *Bioorg. Med. Chem. Lett.*, vol. 20, no. 16, pp. 4865–4869, Aug. 2010, doi: 10.1016/J.BMCL.2010.06.097.

x. M. Verma, A. K. Chaturvedi, A. Chaudhari, and S. S. Parmar, "Monoamine oxidase inhibitory and anticonvulsant properties of 1, 2, 4-trisubstituted 5-imidazolones," *J. Pharm. Sci.*, vol. 63, no. 11, pp. 1740–1744, 1974.

xi. M. S. Mohamed, R. K. Mahmoud, A. I. Sayed, and M. E. El-Araby, "Potent Anticonvulsant 1H-Imidazol-5 (4H)-One Derivatives with Low Neurotoxicity," *Open J. Med. Chem.*, vol. 2, no. 2, p. 24, 2012.

xii. P. K. Naithani, V. K. Srivastava, A. K. Saxena, J. P. Barthwal, T. K. Gupta, and K. Shanker, "Antiparkinsonian activity and dopamine receptor binding studies of imidazolone derivatives.," *Indian J. Exp. Biol.*, vol. 28, no. 12, pp. 1145–1148, 1990.

xiii. T. Lengauer and M. Rarey, "Computational methods for biomolecular docking.," *Curr. Opin. Struct. Biol.*, vol. 6, no. 3, pp. 402–406, Jun. 1996, doi: 10.1016/s0959-440x(96)80061-3.

xiv. D. Veeranna, L. Ramdas, G. Ravi, S. Bujji, V. Thumma, and J. Ramchander, "Synthesis of 1,2,3-Triazole Tethered Indole Derivatives: Evaluation of Anticancer Activity and Molecular Docking Studies," *ChemistrySelect*, vol. 7, no. 29, p. e202201758, Aug. 2022, doi: https://doi.org/10.1002/slct.202201758.

xv. C. M. Venkatachalam, X. Jiang, T. Oldfield, and M. Waldman, "LigandFit: a novel method for the shape-directed rapid docking of ligands to protein active sites.," *J. Mol. Graph. Model.*, vol. 21, no. 4, pp. 289–307, Jan. 2003, doi: 10.1016/s1093-3263(02)00164-x.

xvi. F. Osterberg, G. M. Morris, M. F. Sanner, A. J. Olson, and D. S. Goodsell, "Automated docking to multiple target structures: incorporation of protein mobility and structural water heterogeneity in AutoDock.," *Proteins*, vol. 46, no. 1, pp. 34–40, Jan. 2002, doi: 10.1002/prot.10028.

xvii. U. Abdulfatai, A. Uzairu, and S. Uba, "Molecular docking and quantitative structure-activity relationship study of anticonvulsant activity of aminobenzothiazole derivatives," *Beni-Suef Univ. J. Basic Appl. Sci.*, vol. 7, no. 2, pp. 204–214, Jun. 2018, doi: 10.1016/J.BJBAS.2017.11.002.

xviii. S. Dallakyan and A. J. Olson, "Small-molecule library screening by docking with PyRx," in *Chemical biology*, Springer, 2015, pp. 243–250.

xix. R. A. Friesner *et al.*, "Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy," *J. Med. Chem.*, vol. 47, no. 7, pp. 1739–1749, Mar. 2004, doi: 10.1021/jm0306430.

xx. G. Jones, P. Willett, R. C. Glen, A. R. Leach, and R. Taylor, "Development and validation of a genetic algorithm for flexible docking.," *J. Mol. Biol.*, vol. 267, no. 3, pp. 727–748, Apr. 1997, doi: 10.1006/jmbi.1996.0897.

xxi. Y. Aparna, L. N. Sharada, N. J. P. Subhashini, and S. Sreekanth, "Synthesis, Characterization, Molecular Docking, and Antimicrobial Activity of New Arylidene-Substituted Imidazoles," *Russ. J. Gen. Chem.*, vol. 89, no. 6, pp. 1202–1208, 2019.

xxii. C. Borelli *et al.*, "X-ray structures of Sap1 and Sap5: structural comparison of the

secreted aspartic proteinases from Candida albicans," *Proteins Struct. Funct. Bioinforma.*, vol. 72, no. 4, pp. 1308–1319, 2008.

xxiii. Z. Jin *et al.*, "Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors," *Nature*, vol. 582, no. 7811, pp. 289–293, 2020, doi: 10.1038/s41586-020-2223-y.

xxiv. M. Nagamani, T. Vishnu, P. Jalapathi, and M. Srinivas, "Molecular docking studies on COVID-19 and antibacterial evaluation of newly synthesized 4-(methoxymethyl)-1,2,3-triazolean analogues derived from (E)-1-phenyl-3-(2-(piperidin-1-yl)quinolin-3-yl) prop-2-en-1-one," *J. Iran. Chem. Soc.*, vol. 19, no. 4, pp. 1049–1060, 2022, doi: 10.1007/s13738-021-02365-y.

xxv. N. Umapathi, B. Shankar, M. Raghavender, T. Vishnu, and P. Jalapathi, "Some Novel [6-(Isoxazol-5-ylmethoxy)-3-methylbenzofuran-2-yl]phenylmethanone Derivatives, Their Antimicrobial Activity, and Molecular Docking Studies on COVID-19," *Russ. J. Gen. Chem.*, vol. 91, no. 1, pp. S112–S122, 2021, doi: 10.1134/S1070363222020256.

xxvi. L. Zhang *et al.*, "Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors," *Science (80-.).*, vol. 368, no. 6489, pp. 409–412, Apr. 2020, doi: 10.1126/science.abb3405.

xxvii. C. A. Lipinski, "Lead-and drug-like compounds: the rule-of-five revolution," *Drug Discov. today Technol.*, vol. 1, no. 4, pp. 337–341, 2004.

xxviii. A. Daina, O. Michielin, and V. Zoete, "iLOGP: A Simple, Robust, and Efficient Description of n-Octanol/Water Partition Coefficient for Drug Design Using the GB/SA Approach," *J. Chem. Inf. Model.*, vol. 54, no. 12, pp. 3284–3301, Dec. 2014, doi: 10.1021/ci500467k.

xxix. Y. C. Martin, "A bioavailability score.," *J. Med. Chem.*, vol. 48, no. 9, pp. 3164–3170, May 2005, doi: 10.1021/jm0492002.

xxx. P. Ertl and A. Schuffenhauer, "Estimation of synthetic accessibility score of drug-like molecules based on molecular complexity and fragment contributions," *J. Cheminform.*, vol. 1, no. 1, pp. 1–11, 2009.

xxxi. N. C. Desai, A. M. Bhavsar, and B. B. Baldaniya, "Synthesis and antimicrobial activity of 5-imidazolinone derivatives.," *Indian J. Pharm. Sci.*, vol. 71, no. 1, pp. 90–94, Jan. 2009, doi: 10.4103/0250-474X.51953.

xxxii. A. K. S *et al.*, "Microwave assisted synthesis of N-substituted acridine-1,8-dione derivatives: Evaluation of antimicrobial activity," *J. Heterocycl. Chem.*, vol. 59, no. 7, pp. 1180–1190, 2022, doi: https://doi.org/10.1002/jhet.4458.

xxxiii. A. Daina, O. Michielin, and V. Zoete, "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *Sci. Rep.*, vol. 7, no. 1, pp. 1–13, 2017.

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