Computational Evaluation of Drug-Likeness and ADME Properties of Pyrazole and Chalcone Derivatives

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Abstract

The pyrazole and chalcone derivatives are bioactive molecules that have considerable therapeutic importance. In this study, 16 derivatives were computationally studied using the software of Molinspiration, admetSAR, AI Drug Lab, and vNN-ADMET to analyze their physicochemical properties, druglikeness, and ADMET properties. The Lipinski Rule of Five, along with other druglike filters, was used to screen compounds and identify potential oral medications. Based on the analysis of these compounds compared to curcumin, which acted as the reference molecule, a few compounds exhibited better absorption, permeability, oral bioavailability, and metabolic stability. The toxicity analysis also predicted good safety profiles for these molecules. Compound 11 emerged as the compound with the best balance of pharmacokinetics and toxicity among the studied compounds.

Keywords: Pyrazole derivatives, Chalcone derivatives, ADMET prediction, Drug-likeness, Lipinski rule of five, In silico screening, Pharmacokinetics, Toxicity assessment

INTRODUCTION

Because of their various therapeutic applications, pyrazoles and chalcones belong to two important groups of organic compounds which have received much attention in medicinal chemistry. Pyrazoles are heterocyclic compounds which contain nitrogen, whereas chalcones are natural compounds that are related to flavonoids and possess an α, β-unsaturated carbonyl system. The pharmacological activities of both compound types have been extensively investigated, and they continue to serve as important templates for new therapeutics development.

Computational methods have emerged to be effective and cost-efficient instruments in drug discovery of our modern age [1-3]. They help scientists to make predictions about biological

and pharmacological properties of drugs before carrying out actual experiments. Thus, this kind of approach makes it possible to save much time and money while conducting experiments and to make a preliminary analysis of the properties of a compound. Moreover, in silico analysis allows researchers to rapidly analyze many molecules and select promising leads.

There are several computer-based approaches that enable us to evaluate drug-likeness and pharmacokinetic characteristics of molecules. Calculation of molecular descriptors and prediction of activity parameters belong to common uses of Molinspiration [4]. One of the most popular criteria for assessing the drug-likeness of oral medications based on molecular weight, lipophilicity, hydrogen bond donors, and hydrogen bond acceptors are Lipinski's rule of five [5].

Finally, many scientists apply such software as SwissADME, ADMETSar, AI Drug Lab, and vNN-ADMET to predict absorption, distribution, metabolism, excretion, and toxicity of chemical substances.

Pyrazoles are five-membered heterocyclic rings with two nearby nitrogen atoms. While one nitrogen atom mimics pyridine and functions as a proton acceptor, the other nitrogen atom acts similarly to pyrrole by giving a proton. The amphoteric nature of pyrazoles is facilitated by this special arrangement, which also permits tautomerism and hydrogen-bonding interactions, which have a significant impact on their physicochemical and biological characteristics [6]. The pyrazole ring's substituent actions alter its pharmacological behavior and reactivity [7].

The molecular formula of chalcones is 1,3-diaryl-2-propen-1-one with two phenyl rings connected through an α, β unsaturated carbonyl compound. As a result of the highly conjugated nature of the molecule, chalcones can be chemically modified to form new compounds that exhibit diverse biological activities. Several reports suggest that chalcone derivatives possess antibacterial, antioxidant, anti-inflammatory, anticancer, antimalarial, antileishmanial, and antifungal activities [8-11].

However, having significant pharmacological properties of the pyrazoles and chalcones derivatives is not enough for the successful use of these substances as drugs. There should be good ADMET features, which are essential in developing a pharmaceutical agent. In fact, their usage as drugs might be limited because of low absorption, metabolic problems, insufficient

bioavailability, or toxicity. Hence, evaluation of ADMET features becomes vital for the drug discovery process. Thus, using an efficient tool for the selection of the best compounds among others, with good ADME/T properties, can help develop effective and safe drugs.

For the assessment of drug-likeness and pharmacokinetics of a set of 16 pyrazole and chalcone derivatives, an in silico study was conducted.

METHODOLOGY

Construction of Pyrazoles and Chalcones library

The vast spectrum of biological activities of pyrazoles and chalcones (two among many bioactive substances) is the reason why they play an increasingly important role in medicinal chemistry. Pyrazoles are five membered heterocycles with two adjacent nitrogen atoms in 1,2 positions. Due to their unique structure, pyrazoles are capable of exhibiting strong interactions with various biological targets, hence providing a diverse range of applications in medicine [12]. Chalcones, on the other hand, contain an unsaturated carbonyl group linking two aromatic rings. Due to this structure, they possess high biological activity. Various derivatives of chalcones have been proven to exhibit a number of biological activities, such as antibacterial, antioxidant, anti-inflammatory, antimalarial, antileishmanial, antitumor, and antifungal activities [13-14]. The most promising compounds with favorable therapeutic characteristics were found using a variety of screening criteria, such as Lipinski's rule of five and ADMET prediction studies. Curcumin, a bioactive substance that occurs naturally and has been shown to have therapeutic value, served as a benchmark for comparing the outcomes. Finding possible pyrazole and chalcone compounds with better pharmacokinetic behavior and improved safety profiles over the traditional medication was the study's primary objective.

Probable Drug Properties

The Molinspiration web server, which is an application program based on Java that helps in calculation of chemical properties and predicting bioactivity, was utilized in determination of the drug likeness attributes of chalcone derivatives. Some of the critical physicochemical attributes included MW, topological polar surface area (TPSA), partition coefficient (mLogP), H-bond donor (HBD), H-bond acceptor (HBA), N-rotatable bonds (Nrotb), and molecular volume. In all cases of the studied chalcone compounds, the structure preparation of the

chemicals involved either drawing out the actual structures of the molecules or entering SMILES notation of the molecules. Afterwards, the molecules were analyzed individually.

Table 1 : Physiochemical and Drug-Likeness Evaluation Of 28 Compounds Using Molinspiration

Table 1. Physicochemical and Drug-Likeness Evaluation of 28 Compounds Using Molinspiration

Sr. No.	Compound	milogP	TPSA	Natoms	MW	nON	nOHNH	Nrotb	volume	Nviolations
A	1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Curcumin)	2.3	93.07	27	368.38	6	2	8	332.18	0
1	1,3-diphenylprop-2-en-1-one	3.81	17.07	16	208.26	1	0	3	201.85	0
2	3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-one	4.96	34.9	27	350.42	3	0	5	325.88	0
3	1-(4-chlorophenyl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one	5.65	34.9	28	384.87	3	0	5	339.42	1
4	1-(4-bromophenyl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one	5.76	34.9	28	429.32	3	0	5	343.77	1
5	1-(4-chlorophenyl)-3-[3-(4-methylphenyl)-1-phenyl-1H-pyrazol-4-yl]prop-2-en-1-one	6.08	34.9	29	398.89	3	0	5	355.98	1
6	3-[3-(4-methylphenyl)-1-phenyl-1H-pyrazol-4-yl]-1-phenylprop-2-en-1-one	5.41	34.9	28	364.45	3	0	5	342.44	1
7	1-(4-fluorophenyl)-3-[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one	5.57	34.9	29	382.44	3	0	5	347.37	1
8	3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-yn-1-one	4.61	34.9	27	348.4	3	0	3	320.61	0
9	3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-(4-fluorophenyl)prop-2-yn-1-one	4.77	34.9	28	366.39	3	0	3	325.54	0
10	1-(4-chlorophenyl)-3-[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-yn-1-one	5.74	34.9	29	396.88	3	0	3	350.7	1
11	3-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-phenylprop-2-yn-1-one	4.67	44.13	29	378.43	4	0	4	346.15	0
12	2-chloro-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-(4-fluorophenyl)prop-2-en-1-one	5.45	34.9	29	402.86	3	0	5	344.35	1
13	2-chloro-1-(4-chlorophenyl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one	5.97	34.9	29	419.31	3	0	5	352.95	1
14	2-chloro-1-(4-chlorophenyl)-3-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one	6.65	34.9	30	453.76	3	0	5	366.49	1
15	2-chloro-3-[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-phenylprop-2-en-1-one	5.74	34.9	29	398.89	3	0	5	355.98	1
16	2-chloro-3-[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-methylphenylprop-2-en-1-one	6.19	34.9	30	412.92	3	0	5	372.54	1

ADME Properties

The pharmacokinetic profile of a drug in a biological system is largely dependent on ADME (absorption, distribution, metabolism, and elimination). It is necessary that any potential therapeutic candidate should show favorable ADME properties, so that it can be effective and safe. Some of the major pharmacokinetic properties include aqueous solubility, human intestinal absorption (HIA), P-glycoprotein (P-gp) inhibition, Caco-2 permeability, oral bioavailability, plasma protein binding (PPB), BBB (blood-brain barrier) permeability, and maximum recommended therapeutic dose (MRTD), which were explored in this study for molecules showing compliance with the rule of five formulated by Lipinski (Table 3). Several computational methods like ADMETSar, AI Drug Lab, and vNN-ADMET were utilized to analyze and predict these pharmacokinetics properties [15-16].

Lipinski's rule of Five

Lipinski's rule is a widely used guideline in drug design that helps in predicting whether a compound is likely to possess good oral bioavailability and suitable drug-like properties [17]

According to this rule, A compound should have

- Molecular weight ≤ 500 daltons.
- Log P ≤ 5.
- H-bond acceptors (N or O) ≤ 10.
- Only 5 H-bond donors (-NH or -OH) are allowed
- Only one violation is permitted

Molecular Weight

Molecular weight is a crucial factor in medication design because it influences a compound's absorption and permeability,. A possible medication candidate's molecular weight should typically be less than 500 Da, per the Ghose rule and Lipinski's Rule of Five. Higher molecular weight compounds frequently exhibit low absorption and poor membrane permeability. Only five of the sixteen chalcone derivatives examined had molecular weights within the permissible range, and as a result, they were chosen for additional analysis.

mLogP (Octanol/Water Partition Coefficient)

A compound's lipophilicity is indicated by its mLogP value, which is crucial for membrane permeability, absorption, solubility, and distribution [18]. Compounds with LogP values less than 5 are deemed appropriate for oral medication development, under Lipinski's criteria. Five of the sixteen chalcone derivatives had acceptable mLogP values and were chosen for additional screening.

Hydrogen Bond Donors and Acceptors

Drug-target interaction, solubility, and permeability are greatly influenced by hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA). Good oral bioavailability is more likely to be exhibited by compounds with balanced HBD and HBA values. According to Lipinski's

Rule of Five, five chalcone derivatives in the current investigation met the suggested threshold for both HBD and HBA.

Rotatable Bonds

Covalent bonds not in rings that allow free rotation between atoms and contribute to the overall flexibility of the molecule are referred to as rotatable bonds. Flexibility is an important consideration because it influences factors such as membrane permeability, oral bioavailability, binding affinity, and selectivity for biological targets [19]. If the compound is too flexible, the stability and effectiveness of the potential drug could be adversely impacted. In accordance with Veber's rules and Lipinski's guidelines, molecules with fewer than ten rotatable bonds are considered preferable for oral drug formulation. The rotatable bonds in all the chalcone derivatives under consideration fell within the acceptable limits.

ADME Profile of Selected Pyrazole and Chalcone Derivatives

Absorption Profile

Caco-2 permeability, Human Intestinal Absorption (HIA), aqueous solubility, oral bioavailability, % absorption, and MDCK permeability were some of the parameters that were considered while evaluating the absorption of the selected chalcones [20]. As per the results obtained from AI Drug Lab and ADMETSar, all of the selected molecules had satisfactory absorption characteristics when compared with those of curcumin (Table 3). Compounds 1, 2, 8, 9, and 11 demonstrated excellent intestinal absorption with their HIA values being slightly higher than those of curcumin (i.e., between 73.63% and 74.81% for the selected compounds versus 73.18% for curcumin). Furthermore, compounds 1 and 2 exhibited very high percentage absorption (~100%) as predicted by ADMETSar, whereas compounds 8, 9, and 11 also displayed comparable absorption percentages (97%).

Table 2 : (AI Drug Lab) ADME Profile

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S.No	Parameter	unit	Curcumin	1	2	8	9	11
1	Caco-2	log(cm/s)	-5.28	-5.22	-5.37	-5.39	-5.3	-5.32
2	HIA	%	73.18	73.63	74.74	74.69	74.69	74.81
3	Pgp inhibition	%	44.59	35.27	42.94	45.54	47.46	47.93
4	log $D_{7.4}$	log-ratio	2.02	1.63	1.96	2.02	2.07	1.91
5	Aqeous Solubility	log(mol/L)	-4.67	-4.63	-4.54	-4.73	-4.78	-4.93
6	Oral Bioavailability	%	41.83	46.34	45.51	49.82	50.08	49.34
7	MRTD*	mg/day	373	179	222	215	197	196
	Distribution							
8	BBB	%	20.45	40.52	27.1	30.89	26.73	22.78
9	PPBR	%	57.86	50.55	54.33	58.13	55.42	57.38
10	VDss	L/kg	3.67	3.78	4.32	4.15	4.21	3.66
	Metabolism							
11	CYP2C9 Inhibition	%	40.44	35.03	57.21	63.68	64.48	62.59
12	CYP2D6 Inhibition	%	97.94	96.66	97.83	98.89	99.94	94.82
13	CYP3A4 Inhibition	%	33.89	33.51	33.66	35.07	32.78	40.85
14	CYP2C9 Substrate	%	34.47	36.3	39.09	39.21	36.57	38.12
15	CYP2D6 Substrate	%	61.31	63.43	50.05	50.4	56.92	54.07
16	CYP3A4 Substrate	%	38.29	36.81	34.75	34.34	34.59	34.48
	Excretion							
17	Half Life	hr	55.05	43.58	61.65	62.04	62.27	63.28
18	CL-Hepa	$uLmin^{-1}$ (10^6 cells)$^{-1}$	41.2	51.39	46.24	38.05	36.2	38.48
19	Cl-Micro	mL $min^{-1}g^{-1}$	44.98	30.89	36.58	43.75	45.96	45.9
	Toxicity							
20	hERG Blockers	%	36.68	32.77	41.03	43.65	44.65	46.54
21	Ames	%	37.25	40.87	42.04	47.36	47.62	47.25
22	DILI	%	46.44	42.19	42.48	44.95	47.57	39.29
23	LD50	log(mol/kg)	2.43	2.08	2.2	2.27	2.18	2.18

It is worth noting that positive membrane permeability was verified through the similarity of Caco-2 permeability for all the compounds tested to that of curcumin. It should be noted that all the selected compounds demonstrated improved oral bioavailability values; however, compound 9 had the highest oral bioavailability percentage (50.08%), followed by compounds 8 and 11. Furthermore, the positive membrane permeability of these selected compounds was supported by the MDCK permeability results..

Distribution Profile

BBB permeability, PPBR, volume of distribution (VDss), and inhibitor properties on transporters were the parameters considered in the distribution study [21]. Compared with curcumin, all the selected derivatives were able to penetrate the BBB better based on BBB permeability predictions by the two software packages. While compound 1 displayed the highest BBB permeability value, compound 11 had values similar to those of the conventional drug and would minimize any possible side effects on the CNS. PPBR values for all the derivatives were found to be within the normal limit, indicating balanced interaction with the plasma protein. Although there was reduced PPBR for compounds 1 and 2, compound 8 had

relatively high PPBR when compared to curcumin. Based on VDss values, good distribution was seen in all the derivatives. Inhibitions on transporters, specifically for drugs 8, 9, and 11, revealed moderate to high P-glycoprotein inhibitions.

Metabolism Profile

The combination of HLM, HRM, and UGT substrate properties was evaluated along with CYP450 enzyme inhibition and substrate predictions [23]. Selected compounds had considerable to high inhibition toward the CYP2C9 and CYP2D6 enzymes. Although inhibition towards CYP3A4 was considered moderate in most of the derivatives, compound 8 and 9 had better inhibition against CYP2C9 than curcumin. Compounds 8, 9, and 11 could have more metabolic stability than curcumin based on HLM and HRM results. Moreover, compared to conventional drugs, selected compounds had significantly low UGT substrates, suggesting less metabolite formation and possibly increased biological effect. In conclusion, metabolism studies suggested good metabolic stability and proper enzyme interaction of selected chalcones.

Excretion Profile

Furthermore, the analysis included excretion parameters like half-life, hepatic clearance, microsomal clearance, and mean residence time (MRT). In comparison with curcumin, compound 2, 8, 9, and 11 exhibited higher values of half-lives which implied better retention inside the biological system. Among those four compounds, 11 demonstrated the highest value of half-life, i.e., 63.28 hours.

Lower values of hepatic clearance were seen among compounds 8, 9, and 11 compared with curcumin, implying their better metabolic stability. In terms of the value of MRT, the predicted result for each selected chemical was far less than the value for curcumin which showed balanced distribution/elimination process. Those findings can imply a prolonged effect of the selected compounds.

Toxicity Profile

Toxicity testing was carried out using the Ames test, hERG blocker prediction, drug induced liver injury (DILI) and LD50 test. It was found that Compound 1 exhibited a lower hERG probability of being an hERG blocker than curcumin, which implies a decreased cardiotoxic

potential. Compounds 8, 9, and 11 had slightly increased hERG and Ames values; however, toxicity levels remained within allowable limits.

Compound 11 displayed the smallest DILI score among all tested molecules, which means its ability to induce hepatotoxicity is lower than that of curcumin and other tested derivatives. All compounds showed safe toxicity levels and moderate acute toxicity with LD50 scores comparable to the standard medication.

CONCLUSION

Out of the selected chalcone derivatives, compound 11 emerged as the most promising one for drug development upon considering the entire spectrum of ADME/Tox properties. As compared with the traditional drug, curcumin, compound 11 had a higher oral absorption rate, better bioavailability, good distribution properties, longer half-life, better metabolic stability, and less hepatoxicity. Compound 11 provided a relatively balanced profile in terms of ADME/Tox parameters, despite the slightly better bioavailability of compound 9. Therefore, compound 11 could be regarded as the most promising drug for future study.

References

1. Sahu, T. R., & Sahu, L. (2022). Applications of computational chemistry in drug design: A review. *NeuroQuantology*, *20*(20). https://doi.org/10.48047/NQ.2022.20.20.NQ109321

2. Rocha, M. N. da, Marinho, E. S., Marinho, M. M., & dos Santos, H. S. (2022). Virtual screening in pharmacokinetics, bioactivity, and toxicity of the *Amburana cearensis* secondary metabolites. *Biointerface Research in Applied Chemistry*, *12*(6), 8471–8491. https://doi.org/10.33263/BRIAC126.84718491

3. Xu, W. (2024). Current status of computational approaches for small molecule drug discovery. *Journal of Medicinal Chemistry*, *67*(21), 18633–18636. https://doi.org/10.1021/acs.jmedchem.4c02462

4. Molinspiration Cheminformatics. (n.d.). *Molinspiration property calculation and bioactivity prediction*. http://www.molinspiration.com

5. Lipinski, C. A. (2017). Lead- and drug-like compounds: The rule-of-five revolution. *Nature Reviews Drug Discovery*, *6*(3), 201–203. (Original work published 2007).

6. Küçükgüzel, Ş. G., & Şenkardeş, S. (2015). Recent advances in bioactive pyrazoles. *European Journal of Medicinal Chemistry*, *97*, 786–815. https://doi.org/10.1016/j.ejmech.2014.11.059

7. Sarwar, T., Mustafa, G., Zafar, W., Hassan, A. U., Sumrra, S. H., & Asif, A. (2025). Pyrazoles: A privileged scaffold in drug discovery—Synthetic strategies and pharmacological potential. *Journal of Molecular Structure*, *1348*, 143523.

8. Rammohan, A., Reddy, J. S., & Sravya, G. (2020). Chalcone synthesis, properties and medicinal applications: A review. *Environmental Chemistry Letters*, *18*(2), 433–458. https://doi.org/10.1007/s10311-019-00959-w

9. Constantinescu, T., Lungu, C. N., Jazvinš'cak, M., & Jembrek, J. (2021). Anticancer activity of natural and synthetic chalcones. *International Journal of Molecular Sciences*, *22*(20), Article 11306. https://doi.org/10.3390/ijms222011306

10. Cao, Y., Xu, W., Huang, Y., & Zeng, X. (2020). Licochalcone B: A chalcone derivative from *Glycyrrhiza inflata*, as a multifunctional agent for the treatment of Alzheimer's disease. *Natural Product Research*, *34*(5), 736–739. https://doi.org/10.1080/14786419.2018.1499635

11. Fu, Y., Liu, D., Zeng, H., Ren, X., Song, B., Hu, D., & Gan, X. (2020). New chalcone derivatives: Synthesis, antiviral activity and mechanism of action. *RSC Advances*, *10*(41), 24483–24490. https://doi.org/10.1039/D0RA03723K

12. Kharad, K. B. (2024). A review on biological activities of pyrazole derivatives. *Journal of Chemical Health Risks*, *14*(6), 2816–2822.

13. Ranjan, P., Prakash, R., Chaudhri, V., Pundeer, R. (2021) Hypervalent Iodine(III)-Mediated Monochlorination of Pyrazolyl Chalcone Analogs, *Indian J. Heterocycl. Chem.*, 31, 223–226. (DocID: https://connectjournals.com/01951.2021.31.223

14. Ranjan, P., Prakash, R., Arora, L., Aneja, K.D., Parkash, O. (2017). The Chemistry of α,β-Ditosyloxy Ketones: Hypervalent Iodine (III) Mediated Synthesis of Alkynes from

α,β-Unsaturated Carbonyl Compounds Containing Pyrazole Moiety. *Letters in Organic Chemistry*, *14*(4), 236-242. http://dx.doi.org/10.2174/1570178614666170321121411

15. Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., Lee, P. W., & Tang, Y. (2012a). admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *Journal of Chemical Information and Modeling*, *52*(11), 3099–3105. https://doi.org/10.1021/ci300367a

16. Cheng, F., Li, W., Zhou, Y., Shen, J., Wu, Z., Liu, G., Lee, P. W., & Tang, Y. (2012b). admetSAR: A comprehensive source and free tool for assessment of chemical ADMET properties. *Journal of Chemical Information and Modeling*, *52*(11), 3099–3105. https://doi.org/10.1021/ci300367a

17. Gowtham, H. G., Murali, M., Singh, S. B., Shivamallu, C., Pradeep, S., Shivakumar, C. S., ... & Amruthesh, K. N. (2022). Phytoconstituents of *Withania somnifera* unveiled Ashwagandhanolide as a potential drug targeting breast cancer: Investigations through computational, molecular docking and conceptual DFT studies. *PLoS ONE*, *17*(10), e0275432. https://doi.org/10.1371/journal.pone.0275432

18. Raghav, N., & Mor, N. (2020). Study on enhanced serum protein protecting and anti-cathepsin activities of various curcumin formulations containing traditional excipients and bio-enhancers. *Bioorganic Chemistry*, *104*, 104177. https://doi.org/10.1016/j.bioorg.2020.104177

19. Hughes, J. D., Blagg, J., Price, D. A., Bailey, S., DeHauen, S. A., Gaizauskas, E., ... & Reicze, A. D. (2008). Physiochemical drug properties associated with in vivo toxicological outcomes. *Bioorganic & Medicinal Chemistry Letters*, *18*(17), 4872–4875. https://doi.org/10.1016/j.bmcl.2008.07.071

20. Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting pharmacokinetic properties using graph-based signatures. *Journal of Medicinal Chemistry*, *58*(9), 4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104

21. Banks, W. A. (2016). From blood-brain barrier to blood-brain interface: New opportunities for CNS drug delivery. *Nature Reviews Drug Discovery*, *15*(3), 32–38.

(Original journal entry cited as *Drug Discovery Today*, *21*(1), 32–38). https://doi.org/10.1016/j.drudis.2015.08.007

22. Aggarwal, S., Raghav, N., Dahiya, H., & Mor, N. (2025). A virtual screening of *Withania somnifera* compounds using ADMET predictions, molecular docking, MD simulation and DFT calculations: Withasomniferol C an effective drug and potent inhibitor of anti-inflammatory targets. *Computational Biology and Chemistry*, *118*, 108488. https://doi.org/10.1016/j.compbiolchem.2024.108488

23. Ekins, S., & Lattman, M. (2018). Cytochrome P450 inhibitors: A review of structural and functional diversity. *Drug Metabolism Reviews*, *50*(3), 338–350.