Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

Research Article

In silico ADMET Screening of some Imidazo-thiadiazole based ChalconeDerivatives to be developed as Potent EGFR Inhibitors for the Treatment of Cancer

Abhinandan A. Alman[1*], Vishal Soni[2], Suresh G. Killedar[3]

[*1]Ph.D. Research scholar, B.R. Nahata College of Pharmacy, Department of Pharmacy, Mandsaur University, Mandsaur. Madhya Pradesh, 458001, India. Email: nandanvan0088@gmail.com.

[2]Associate Professor, Faculty of Pharmacy, Mandsaur University, Mandsaur. Madhya Pradesh, 458001, India.

[3]Professor & Principal, SantGajananMaharaj College of Pharmacy, Mahagaon, Shivaji University, Kolhapur, Maharashtra, 416503, India.

Received: 17 Nov 2021; Revised: 12 Dec 2021; Accepted and Published: 20 Dec 2021

Abstract

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET), play key roles in drug discovery and development. A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at a therapeutic dose.A lot of *in silico* models are developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties. In present study, we have designed some imidazo-thiadiazole based Chalcone derivatives to be developed as potential EGFR inhibitors for the treatment of cancer.The designed derivatives were screened through Lipinski rule, Veber's rule, ADMET analysis, and drug-likeness properties. We concluded that all the compounds **10a, 10b, 10c, 10d, 10e, 10f, 10g, 10h, 10i, 10j, 10k, 10l, 10m, 10n, 10o, 10p**were found to possess drug-likeness properties and can be developed further to get more promising molecules for the treatment of cancer. In near future, we are aiming to report molecular docking studies of the designed compounds followed by synthesis and biological evaluation.

Keywords: Imidazo-thiadiazoles, Chalcones, EGFR, ADMET, Cancer

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

Introduction

Although radiotherapy and chemotherapy treat a broad range of tumors indiscriminately, molecular targeting therapies for cancer treatment have the ability to have greater tumor precision. Over the past few decades, significant progress has been made in identifying the complex cellular, biochemical, and genetic pathways that lead to cancer development and progression(1). This enhanced mechanistic knowledge of cancer has aided in the design, growth, and clinical testing of more tumor-specific anticancer treatment approaches. Tyrosine kinases are known to play a role in tumor growth and proliferation, and they have become common drug targets. Tyrosine kinase inhibitors (TKIs) prohibit associated kinases from phosphorylating tyrosine residues in their substrates, preventing downstream signaling pathways from being activated(2). Multiple robust and well-tolerated TKIs targeting single or multiple targets, including EGFR, ALK, ROS1, HER2, NTRK, VEGFR, RET, MET, MEK, FGFR, PDGFR, and KIT, have been developed over the last two decades, contributing to our understanding of precision cancer medicine based on a patient's genetic alteration profile(3). Some promising cancer treatments have focused on the epidermal growth factor receptor (EGFR) as a molecular target. The EGFR family consists of four transmembrane tyrosine kinases (EGFR1/ErbB1, Her2/ErbB2, Her3/ErbB3, and Her4/ErbB4), as well as thirteen secreted polypeptide ligands(4). EGFRs are overexpressed in multiple solid tumors, including breast, pancreas, head and neck, kidney, vaginal, renal, colon, and non-small-cell lung cancer(5). Overexpression of these genes stimulates downstream signaling channels, causing cell proliferation, differentiation, cell cycle progression, angiogenesis, cell motility, and apoptosis inhibition(6). If the knowledge of the role of EGFR signaling networks in tumor activity progresses, we would be able to quantify its specific functions more precisely. EGFRs' high expression and/or adaptive activation coincides with the pathogenesis and development of many tumors, making them appealing candidates for both diagnosis and therapy. Several strategies for targeting these receptors and/or the EGFR-mediated effects in cancer cells have been established. EGFRIs are classified into two classes: monoclonal antibodies (mAbs) that specifically target the EGFR extracellular domain, such as cetuximab (Erbitux), and small molecule TKIs that specifically target the EGFR catalytic domain, such as gefitinib (Iressa) and erlotinib (Tarceva)(7–11).

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

Chalcones are naturally occurring pharmacologically active compounds which possesses variety of important biological activities. Heterocyclic derivatives of chalcone exhibits anticancer potential against numerous cancer cell lines through different mechanisms. Anticancer chalcone derivatives exhibits and improve the anticancer characteristics by adopting different approaches such as structural and functional manipulation along with substitution of aryl rings(12–16). Molecular hybridization and replacement in their structure with pharmacological important moieties has been useful for development of novel medicinal agent which shows significant anticancer properties with lesser toxicity. Evolution of new hybrid chalcone analogues occurred through the linkage between efficient chalcone with different adequate and prominent anticancer scaffold like thiadiazole, coumarine, benzothiazole and imidazole which have verified and proved inherent pharmacological role(17–20). However, chalcones performs a leading appearance in medicinal chemistry but utilization of their pharmacological potential still not enough. ADME features are essential for regulatory approval since they help drug researchers comprehend a medication candidate's safety and effectiveness.A lot of *in silico* models are hence developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties(21–28).In the present work we have performed *in silico* ADMET screening of designed imidazo-thiadiazole based Chalcone derivatives to be developed as potential EGFR inhibitors for the treatment of cancer. All the designed derivatives were subjected for the calculations of different ADMET parameters to select most promising compound which can possess more drug-likeness properties.

Material and Methods

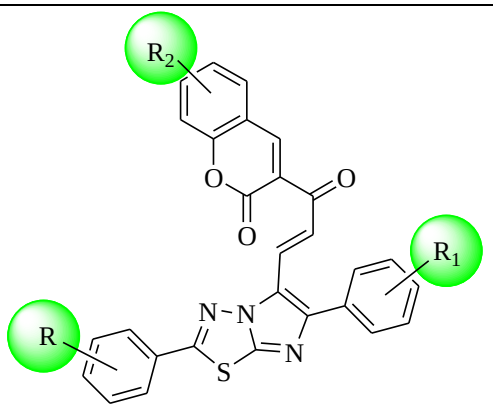
Designing of Chalcone derivatives

One step acylation and cyclization reaction was achieved by heating the carboxylic acid with thiosemicarbazide in the presence of phosphorus halide.*N*-4-Phenacyl 1,2,4-thiadiazolium salts, which are usually prepared by reacting phenacyl bromide with 5-Substituted 2-Amino-1,3,4-thiadiazole, undergo internal cyclization to give fused imidazole derivatives.The vilsmeier-haack reaction of electron rich aromatic compounds, generally, affords aldehyde derivatives in good yields. This reaction will be carried out in presence of DMF and $POCl_3$. Base catalyzed condensation reaction between substituted salicylaldehyde and ethyl aceto acetate to yield 3-acetyl

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

coumarin.Substituted chalcone derivatives are generally carried out on basis of Claisen- Schmidt reaction using strong base such as NaOH or KOH in polar solvents like DMF or alcohol. The structure of the parent compound and the substituted chalcone derivatives are depicted in Table 1.

Table 1. Imidazo-thiadiazole based Chalcone derivatives



Code	R	R_1	R_2
10a	H	H	H
10b	H	4-OCH_3	H
10c	H	H	5-Cl
10d	4-Cl	H	H
10e	4-Cl	4-OCH_3	H
10f	4-OCH_3	H	5-Cl
10g	4-OCH_3	H	H
10h	4-NO_2	H	H
10i	4-NH_2	H	H
10j	4-CH_3	H	5-Cl
10k	4-Br	H	H
10l	3-NO_2	H	H
10m	3-NH_2	H	H
10n	2,4-Cl	H	H
10o	3,5-NO_2	H	H
10p	2-I	H	H

Pharmacokinetics and toxicity predictions of designed derivatives

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET), play key roles in drug discovery and development. A high-quality drug candidate should not only have sufficient efficacy against the therapeutic target, but also show appropriate ADMET properties at a therapeutic dose.The designed derivatives were screened for its ADME analysis, drug-likeliness and toxicity parameters. The Lipinski rule of five and the pharmacokinetic (ADME) characteristics of designed derivatives were investigated using SwissADME(29) servers. The

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

toxicity of the compounds has been predicted using ProTox-II, which is a freely accessible webserver for *in silico* toxicity predictions of new derivatives (http://tox.charite.de/protox_II)(30).

Results

Pharmacokinetic characteristics are critical to drug development because they enable scientists to investigate the biological impacts of possible pharmacological candidates(23). This compound's oral bioavailability was evaluated using Lipinski's rule of five and Veber's rules (Table 2). To better understand the pharmacokinetics profiles and drug-likeness properties of the proposed compounds, the ADME characteristics of all of them were examined (Table 3). Fig. 3 depicts the physicochemical domain that is ideal for oral bioavailability. The oral acute toxicity have been predicted along with LD_{50} (mg/kg), toxicity class, hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity (Table 4).

Table 2. Lipinski rule of 5 and Veber's rule calculated for molecules

Compound Codes	Lipinski rule of five					Veber's rule	
	Log P	Mol. Wt.	HBA	HBD	Violations	Total polar surface area (Å^2)	No. of rotatable bonds
10a	5.3	475.52	5	0	0	105.71	5
10b	5.17	505.54	6	0	1	114.94	6
10c	5.67	509.96	5	0	1	105.71	5
10d	4.71	509.96	5	0	2	105.71	5
10e	5.72	539.99	6	0	1	114.94	6
10f	5.35	505.54	6	0	1	114.94	6
10g	5.87	539.99	6	0	1	114.94	6
10h	4.69	520.52	7	0	1	151.53	6
10i	4.7	490.53	5	1	0	131.73	5
10j	5.55	489.54	5	0	0	105.71	5
10k	5.85	554.41	5	0	2	105.71	5
10l	4.73	520.52	7	0	1	151.53	6
10m	4.7	490.53	5	1	0	131.73	5
10n	6.36	544.41	5	0	2	105.71	5
10o	3.92	565.51	9	0	2	197.35	7
10p	5.85	601.41	5	0	2	105.71	5

Where: Mol. Wt., molecular weight; HBA, hydrogen bond acceptors; HBD, hydrogen bond donors

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

Table 3. The pharmacokinetics and drug-likeness properties of developed compounds

Compound codes	Pharmacokinetics									Drug-likeness			
	GI abs.	BBB pen.	P-gp sub.	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Log K_p (skin permeation, cm/s)	Ghose	Egan	Muegge	Bioavailability Score
				Inhibitors									
10a	Low	No	No	No	No	Yes	No	No	-4.82	2	1	1	0.55
10b	Low	No	No	No	No	Yes	No	No	-5.02	3	1	1	0.55
10c	Low	No	No	No	No	No	No	No	-4.58	3	1	1	0.55
10d	Low	No	No	No	Yes	No	No	No	-5.63	3	1	1	0.17
10e	Low	No	No	No	No	Yes	No	No	-4.79	3	1	1	0.55
10f	Low	No	No	No	No	Yes	No	No	-5.02	3	1	1	0.55
10g	Low	No	No	No	No	No	No	No	-4.79	3	1	1	0.55
10h	Low	No	No	No	No	No	No	No	-5.22	3	2	2	0.55
10i	Low	No	No	No	No	Yes	No	No	-5.39	3	1	1	0.55
10j	Low	No	No	No	No	No	No	No	-4.64	3	1	1	0.55
10k	Low	No	No	No	No	No	No	No	-4.81	3	1	1	0.17
10l	Low	No	No	No	No	No	No	No	-5.22	3	2	2	0.55
10m	Low	No	No	No	No	Yes	No	No	-5.39	3	1	1	0.55
10n	Low	No	No	No	No	No	No	No	-4.35	3	1	1	0.17
10o	Low	No	No	No	No	No	No	Yes	-5.61	3	1	2	0.17
10 p	Low	No	No	No	No	No	No	No	-5.13	3	1	2	0.17

Where: NL, Native ligand; GI abs., gastrointestinal absorption; BBB pen., blood brain barrier penetration; P-gp sub., p-glycoprotein substrate

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

Table 3. The predicted acute toxicity of molecules

Comp codes	Parameters							
	LD_{50} (mg/kg)	Tox. class	Prediction accuracy (%)	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
				(Probability)				
10a	1000	4	23	A (0.56)	I (0.53)	I (0.64)	I (0.57)	I (0.61)
10b	1000	4	23	A (0.54)	I (0.54)	A (0.84)	A (0.52)	I (0.68)
10c	1000	4	23	A (0.58)	I (0.62)	I (0.59)	I (0.57)	I (0.60)
10d	1000	4	23	A (0.58)	I (0.62)	I (0.58)	I (0.57)	I (0.60)
10e	1000	4	23	A (0.58)	I (0.60)	A (0.96)	I (0.51)	I (0.61)
10f	1000	4	23	A (0.54)	I (0.64)	A (0.84)	A (0.52)	I (0.68)
10g	1000	4	23	A (0.58)	I (0.60)	A(0.87)	I (0.51)	I (0.61)
10h	1000	4	23	A (0.51)	A (0.70)	A(0.67)	A (0.90)	I (0.73)
10i	1000	4	23	A (0.57)	A (0.63)	I (0.65)	A (0.53)	I (0.70)
10j	1000	4	23	A (0.55)	I (0.52)	I (0.82)	I (0.56)	I (0.63)
10k	1000	4	23	A (0.61)	I (0.62)	A (0.68)	I (0.57)	I (0.57)
10l	1000	4	23	A (0.51)	A (0.70)	A(0.65)	A (0.90)	I (0.73)
10m	1000	4	23	A (0.57)	A (0.63)	I (0.72)	A (0.53)	I (0.70)
10n	1000	4	23	A (0.58)	I (0.62)	A (0.82)	I (0.57)	I (0.60)
10o	1000	4	23	A (0.51)	A (0.70)	A (0.59)	A (0.90)	I (0.73)
10p	1000	4	23	A (0.60)	I (0.62)	A (0.58)	I (0.58)	I (0.57)

Where: I, Inactive; A, Active

Discussion

In present study we have designed and developed some imidazo-thiadiazole based Chalcone derivativesas potential EGFR inhibitors. In accordance with Lipinski's and Veber's rule (Table 2). The log P values of all the molecules were between the ranges 3.92 to 6.36 which indicate optimum lipophilicity. Lipophilicity is a significant feature of the molecule that affects how it works in the body(27). It is determined by the compound's Log P value, which measures the drug's permeability in the body to reach the target tissue(31,32). The molecular weight of all the molecules was around 500 Da which indicates active better transport of the molecules through biological membrane. Fortunately, the Lipinski rule of 5 had not been compromised by the compounds(23,24). All the compounds except 10a, 10i, 10j and 10m violated theLipinski rule of 5 .The total polar surface area (TPSA) and the number of rotatable bonds have been found to better discriminate between compounds that are orally active or not. According to Veber's rule, TPSA should be $\leq$ 140 and number of rotatable bonds should be $\leq$ 10. It was observed that compounds 10h, 10l and 10o violated the Veber's rule, as it has TPSA 151$Å^2$, 197$Å^2$respectively.

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

In order to further optimize the compounds, pharmacokinetics and drug-likeness properties were calculated for each one. All the compounds showed no penetration to the blood-brain barrier (BBB). The log *Kp* (skin penetration, cm/s) and bioavailability values of all the compounds were within acceptable limits. (Table 3).The GI absorption of all the compounds was found to be low.

In acute toxicity predictions, class-III i.e. toxic if swallowed ($50<LD_{50}\leq300$), toxicity class-IV which means harmful if swallowed ($300<LD_{50}\leq2000$), class-V which indicate may be harmful if swallowed ($2000<LD_{50}\leq5000$)(30). From this virtual screening, it was concluded that all the compounds fall in class IV of toxicity, which means they possess drug-like properties and hence were subjected to molecular docking studies.

Conclusion

A lot of *in silico* models are developed for prediction of chemical ADMET properties. However, it is still not easy to evaluate the drug-likeness of compounds in terms of so many ADMET properties. In present study, we have designed some imidazo-thiadiazole based Chalcone derivatives to be developed as potential EGFR inhibitors for the treatment of cancer.The designed derivatives were screened through Lipinski rule, Veber's rule, ADMET analysis, and drug-likeness properties. We concluded that all the compounds **10a, 10b, 10c, 10d, 10e, 10f, 10g, 10h, 10i, 10j, 10k, 10l, 10m, 10n, 10o, 10p**were found to possess drug-likeness properties and can be developed further to get more promising molecules for the treatment of cancer. In near future, we are aiming to report molecular docking studies of the designed compounds followed by synthesis and biological evaluation.

References

1. Chan DLH, Segelov E, Wong RSH, Smith A, Herbertson RA, Li BT, et al. Epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer. Vol. 2017, Cochrane Database of Systematic Reviews. 2017.
2. Grünwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. Vol. 95, Journal of the National Cancer Institute. 2003. p. 851–67.
3. Song Z, Ge Y, Wang C, Huang S, Shu X, Liu K, et al. Challenges and perspectives on the development of small-molecule EGFR inhibitors against T790M-mediated resistance in non-small-cell lung cancer: Miniperspective. Vol. 59, Journal of Medicinal Chemistry. 2016. p. 6580–

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

94.

4. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. Vol. 11, Endocrine-Related Cancer. 2004. p. 689–708.
5. Woodburn JR. The epidermal growth factor receptor and its inhibition in cancer therapy. In: Pharmacology and Therapeutics. 1999. p. 241–50.
6. Chen L, Fu W, Zheng L, Liu Z, Liang G. Recent Progress of Small-Molecule Epidermal Growth Factor Receptor (EGFR) Inhibitors against C797S Resistance in Non-Small-Cell Lung Cancer. Vol. 61, Journal of Medicinal Chemistry. 2018. p. 4290–300.
7. Attili I, Karachaliou N, Conte PF, Bonanno L, Rosell R. Therapeutic approaches for T790M mutation positive non-small-cell lung cancer. Expert Rev Anticancer Ther. 2018;18(10):1021–30.
8. Ai X, Guo X, Wang J, Stancu AL, Joslin PMN, Zhang D, et al. Targeted therapies for advanced non-small cell lung cancer. Oncotarget. 2018;9(101):37589–607.
9. Bryce AH, Rao R, Sarkaria J, Reid JM, Qi Y, Qin R, et al. Phase i study of temsirolimus in combination with EKB-569 in patients with advanced solid tumors. Invest New Drugs. 2012;30(5):1934–41.
10. Grünwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. J Natl Cancer Inst. 2003;95(12):851–67.
11. Roskoski R. Cyclin-dependent protein kinase inhibitors including palbociclib as anticancer drugs. Pharmacol Res [Internet]. 2016;107:249–75. Available from: http://dx.doi.org/10.1016/j.phrs.2016.03.012
12. Gokhale N, Dalimba U, Kumsi M. Facile synthesis of indole-pyrimidine hybrids and evaluation of their anticancer and antimicrobial activity. J Saudi Chem Soc [Internet]. 2017;21(7):761–75. Available from: http://dx.doi.org/10.1016/j.jscs.2015.09.003
13. Saavedra LM, Ruiz D, Romanelli GP, Duchowicz PR. Quantitative Structure-Antifungal Activity Relationships for cinnamate derivatives. Ecotoxicol Environ Saf [Internet]. 2015;122:521–7. Available from: http://dx.doi.org/10.1016/j.ecoenv.2015.09.024
14. Lv PC, Li DD, Li QS, Lu X, Xiao ZP, Zhu HL. Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives as EGFR TK inhibitors and potential anticancer agents. Bioorganic Med Chem Lett. 2011;21(18):5374–7.
15. Bhadoriya KS, Kumawat NK, Bhavthankar S V., Avchar MH, Dhumal DM, Patil SD, et al. Exploring 2D and 3D QSARs of benzimidazole derivatives as transient receptor potential melastatin 8 (TRPM8) antagonists using MLR and kNN-MFA methodology. J Saudi Chem Soc [Internet]. 2016;20:S256–70. Available from: http://dx.doi.org/10.1016/j.jscs.2012.11.001

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

16. Galayev O, Garazd Y, Garazd M, Lesyk R. Synthesis and anticancer activity of 6-heteroarylcoumarins. Eur J Med Chem [Internet]. 2015;105:171–81. Available from: http://dx.doi.org/10.1016/j.ejmech.2015.10.021
17. Akhtar W, Khan MF, Verma G, Shaquiquzzaman M, Rizvi MA, Mehdi SH, et al. Therapeutic evolution of benzimidazole derivatives in the last quinquennial period. Eur J Med Chem [Internet]. 2017;126:705–53. Available from: http://dx.doi.org/10.1016/j.ejmech.2016.12.010
18. Mohana Roopan S, Sompalle R. Synthetic chemistry of pyrimidines and fused pyrimidines: A review. Synth Commun. 2016;46(8):645–72.
19. Gil A, Pabón A, Galiano S, Burguete A, Pérez-Silanes S, Deharo E, et al. Synthesis, biological evaluation and structure-activity relationships of new quinoxaline derivatives as anti-Plasmodium falciparum agents. Molecules. 2014;19(2):2166–80.
20. Ghorab MM, Ragab FA, Heiba HI, El-Gazzar MG, Zahran SS. Synthesis, anticancer and radiosensitizing evaluation of some novel sulfonamide derivatives. Eur J Med Chem [Internet]. 2015;92:682–92. Available from: http://dx.doi.org/10.1016/j.ejmech.2015.01.036
21. Khan SL, Siddiqui FA, Shaikh MS, Nema N V., Shaikh AA. Discovery of potential inhibitors of the receptor-binding domain (RBD) of pandemic disease-causing SARS-CoV-2 Spike Glycoprotein from Triphala through molecular docking. Curr Chinese Chem [Internet]. 2021;01. Available from: https://www.eurekaselect.com/192390/article
22. Siddiqui FA, Khan SL, Marathe RP, Nema N V. Design, Synthesis, and In Silico Studies of Novel N-(2-Aminophenyl)-2,3- Diphenylquinoxaline-6-Sulfonamide Derivatives Targeting Receptor-Binding Domain (RBD) of SARS-CoV-2 Spike Glycoprotein and their Evaluation as Antimicrobial and Antimalarial Agents. Lett Drug Des Discov [Internet]. 2021;18(9):915–31. Available from: https://doi.org/10.2174/1570180818666210427095203
23. Khan A, Unnisa A, Sohel M, Date M, Panpaliya N, Saboo SG, et al. Investigation of phytoconstituents of Enicostemma littorale as potential glucokinase activators through molecular docking for the treatment of type 2 diabetes mellitus. Silico Pharmacol [Internet]. 2022;10(1). Available from: https://doi.org/10.1007/s40203-021-00116-8
24. Shntaif AH, Khan S, Tapadiya G, Chettupalli A, Saboo S, Shaikh MS, et al. Rational drug design, synthesis, and biological evaluation of novel N-(2-arylaminophenyl)-2,3-diphenylquinoxaline-6-sulfonamides as potential antimalarial, antifungal, and antibacterial agents. Digit Chinese Med [Internet]. 2021;4(4):290–304. Available from: https://www.sciencedirect.com/science/article/pii/S2589377721000483
25. Khan, Sharuk L; Siddiui FA. Beta-Sitosterol: As Immunostimulant, Antioxidant and Inhibitor of

ISSN: 0975-3583,0976-2833 VOL12,ISSUE06,2021

SARS-CoV-2 Spike Glycoprotein. Arch Pharmacol Ther. 2020;2(1).

26. Chaudhari RN, Khan SL, Chaudhary RS, Jain SP, Siddiqui FA. B-Sitosterol: Isolation from Muntingia Calabura Linn Bark Extract, Structural Elucidation And Molecular Docking Studies As Potential Inhibitor of SARS-CoV-2 Mpro (COVID-19). Asian J Pharm Clin Res. 2020;13(5):204–9.
27. Khan S, Kale M, Siddiqui F, Nema N. Novel pyrimidine-benzimidazole hybrids with antibacterial and antifungal properties and potential inhibition of SARS-CoV-2 main protease and spike glycoprotein. Digit Chinese Med. 2021;4(2):102–19.
28. Khan SL, Sonwane GM, Siddiqui FA, Jain SP, Kale MA, Borkar VS. Discovery of Naturally Occurring Flavonoids as Human Cytochrome P450 (CYP3A4) Inhibitors with the Aid of Computational Chemistry. Indo Glob J Pharm Sci. 2020;10(04):58–69.
29. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7.
30. Banerjee P, Eckert AO, Schrey AK, Preissner R. ProTox-II: A webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018;46(W1):W257–63.
31. Krzywinski M, Altman N. Points of significance: Significance, P values and t-tests. Nat Methods. 2013;10(11):1041–2.
32. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Vol. 64, Advanced Drug Delivery Reviews. 2012. p. 4–17.