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ASSESSING THE DRUG ABILITY OF CHALCONES USING IN- SILICO TOOLS

Shaheen begum*

Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Technology,Sri Padmavathi Mahila Visvavidyalayam (Women's University),Tirupathi 517502,Andhra Pradesh, India.

***Corresponding Author Email: shaheen.pharmchem@gmail.com**

ABSTRACT

*Chalcones are very well known natural as well as synthetic compounds associated with diverse set of pharmacological activities. They have the potential to be developed as lead compounds for the discovery of antioxidant, anti-inflammatory and anticancer agents. Naturally occurring and synthetic chalcone compounds have shown safety profiles in clinical trials. To study impact of substitutions on drug-likeliness and ADME profile of chalcones, twenty chalcones were selected from literature and molecular properties such as partition coefficient (Log P) , molecular weight, number of H-bond acceptors and donors, molecular polar surface area(TPSA) and number of rotatable bonds were calculated using molinspiration software available on the website: http://www.molinspiration.com/cgi-bin/properties.ADME profile has been obtained using pre ADMET free online tool (preADMET). Results clearly demonstrated that all chalcones have very good oral absorption and oral bioavailability. It is also observed that 4-acetamido substitution had decreased chalcones permeability in to CNS. In vitro plasma protein binding of 4-acetamido chalcones is less when compared to other chalcones. Compounds **1-20** showed % HIA ranging from 95.58 to 100% and all compounds showed optimum Caco-2 cell permeability (19.15-56.39 nm/sec). Seven out of twenty chalcones (**1,2,4,6,7,10,20**) displayed optimum MDCK cell permeability (25-500 nm/sec). 4-acetamido group introduction on chalcone had a great impact on the physicochemical and ADME profile of these molecules.*

KEY WORDS

Chalcones, Drug likeliness, Molinspiration, ADME, LogP, MDCK cell permeability, Caco-2 cell permeability, TPSA, preADMET

INTRODUCTION

Lipinski's Rule of Five (Ro5) which stipulates limits for certain parameters for good oral absorbtion or permeability is considered as the first systemic guidelines in medicinal chemistry [1]. This rule predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight (M.Wt) is greater than 500 and the calculated Log P (CLogP) is greater than 5 (or MlogP.4.15)[2].Many related rules have been subsequently modified and proposed as the "Rule-of-Three", which defines fragment properties with an average molecular weight 300 Da, Clog P 3, the number of hydrogen bond donors 3, the number of hydrogen bond acceptors 3, and the number of rotatable bonds < 3. Recently, Pfizer's "Rule of 3/75" has been described which states that compounds with a calculated partition coefficient (ClogP) of < 3 and topological polar surface area (TPSA) > 75 have the best chances of being well tolerated from a safety perspective *in vivo*[3].

The concept of drug-likeness has been introduced to determine the characteristics necessary for a drug to be successful. It helps to optimize

pharmacokinetic and pharmaceutical properties, for example, solubility, chemical stability, bioavailability and distribution profile [4]. Drug-likeness can be calculated based on the molecular descriptors as per Lipinski's "Rule-of-Five". Many *in silico* tools can be used to design libraries of compounds with drug-like properties [3]. With the use of *in silico* tools it is possible to predict drug-likeliness and pharmacokinetic or ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) profile, drug safety and drug-drug interactions, thereby accelerate the drug discovery process[2].

Chalcone is a versatile template that is linked with several important biological activities such as antioxidant, anticancer, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antimalarial, antileishmanial, antihyperglycemic, activity etc[5]. Chalcones (1, 3-Diphenyl-2-propen-1-one) have a three-carbon α, β-unsaturated carbonyl system and have potential to inhibit enzyme systems [6]. Chalcones have sufficient lipophilicity to cross blood brain barrier and have been proposed to play a useful role in protecting the central nervous system against oxidative and excitotoxic stress [7]. In the present paper twenty chalcones (Table.1) were selected from the literature [8,9]and their drug likeness,ADME parameters were predicted using *in-silico* tools. As much useful and relevant information as possible on the structural features and physicochemical properties of chalcones have been acquired. Influence of various parameters on absorption,metabolism and their ability to penetrate in to brain were reported.

MATERIALS AND METHODS

Lipinski's rule of five is versatile to evaluate drug likeness properties [10]. Molinspiration, web based software was used to obtain physicochemical properties such as LogP, TPSA, drug likeness (http://www.molinspiration.com/cgi-bin/properties last accessed on 28th Dec 2015). Log P parameter is used to check good permeability across the cell membrane. Molecular polar surface area (TPSA) is a very useful parameter to predict the transport properties of drugs like intestinal absorption and blood-brain barrier penetration. TPSA and molecular volume is inversely proportional to percentage absorption (%ABS). Therefore, it allows prediction of transport properties of drugs in the intestines and blood-brain barrier crossing.

The polar surface area (PSA) of a molecule is a useful descriptor for the optimization of drugs ability to permeate cells.This has been calculated as Topological polar surface area (TPSA), which is recognized as a good indicator of drug absorption in the intestine. Topological polar surface area was used to calculate the percentage of Absorption (%ABS) according to the equation: %ABS =109 – [0.345× TPSA] [11]. Number of rotatable bonds measures molecular flexibility and proved to be a very good descriptor of absorption and bioavailbility of drugs.

In vitro %HIA, Caco2 and MDCK cell permeabilities, plasma protein binding and blood-brain barrier penetration values of chalcones were obtained from ADME calculator (http://www.preadmet.bmdc.org/index.php last accessed on 8th Feb, 2015).

RESULTS AND DISCUSISON

All twenty chalcones have very good absorption in the system (Table 1, 2). Drug likeliness is attributed to chalcones when they are substituted with acetamido group at 4th position. It is evident from Table.3 that all 4-acetamido chalcones have obeyed Lipinski's rule. Clog P of these compounds were found below 5, suggesting good permeability across cell membrane. Two compounds (**13, 17**) have 6 rotatable bonds that is they have more conformational flexibility than others. All the compounds can easily bind to the receptor as *n* violatios =1 or <0 for the given set of compounds. It was observed that all the title compounds exhibited good %absorption ranging from 77.26 to 103.11%. Oral drug absorption can be predicted using *in vitro* models like human intestinal absorption (%HIA), Caco2 cell (PCaco2) and MDCK cell (PMDCK) permeabilities (Table 4, 5). Compounds **1-20** showed % HIA ranging from 95.58 to 100% and all compounds showed optimum Caco2 cell permeability (19.15-56.39 nm/sec). Seven out of twenty chalcones (**1,2,4,6,7,10,20**) displayed optimum MDCK cell permeability (25-500 nm/sec).Except chalcones **13,17,19,20,** others have optimum penetration into CNS via the blood-brain barrier.It is also observed that 4-acetamido substitution had decreased chalcones permeability in to CNS. In vitro plasma protein binding of 4-acetamido chalcones is less when compared to other chalcones.It can be concluded that 4-acetamido group introduction on chalcone had a great impact on the physicochemical and ADME profile of these molecules.

Table.1 Physicochemical data of chalcones

Chalcone	R_1	R_2	Melting point
1	4-H	4-H	119-122
2	4-H	3,4(-Cl)$_2$	96-100
3	4-N(CH$_3$)$_2$	3,4(-Cl)$_2$	124-126
4	4-Cl	4-Cl	160-163
5	4-Cl	3,4(-Cl)$_2$	120-123
6	4-CH$_3$	4-Cl	159-162
7	4-Cl	4-H	122-125
8	4-Cl	4-Br	168-170
9	4-CH$_3$	4-H	95.6-100
10	4-H	4-Cl	85-92
11	4-H	4-Br	155-160
12	4-H	4-NHCOCH$_3$	161.7-162.2
13	4-OCH$_3$	4-NHCOCH$_3$	206.5-207
14	4-CH$_3$	4-NHCOCH$_3$	197.5-199
15	4-Cl	4-NHCOCH$_3$	215-215.7
16	3,4(-Cl)$_2$	4-NHCOCH$_3$	210.4-211
17	4-NO$_2$	4-NHCOCH$_3$	239.7-241
18	4-N(CH$_3$)$_2$	4-NHCOCH$_3$	150.9-154.7
19	Thiophene(ring B)	4-NHCOCH$_3$	147.8-149.3
20	Furan (ring B)	4-NHCOCH$_3$	118-119

Table 2: Prediction of the molecular properties for chalcones and derivatives (1-10)

S.No	CLogP	M.Wt	HBA	HBD	nVio	nrotb	Volume	TPSA	%ABS
1	4.082	222.28	1	0	0	4	218.65	17.071	103.11
2	**5.366**	291.17	1	0	1	4	245.72	17.071	103.11
3	**5.468**	334.24	2	0	1	5	291.63	20.309	101.99
4	**5.438**	291.17	1	0	1	4	245.72	17.071	103.11
5	**6.044**	325.62	1	0	1	4	259.26	17.071	103.11
6	**5.208**	270.75	1	0	1	4	248.75	17.071	103.11
7	4.76	256.73	1	0	0	4	232.19	17.071	103.11
8	**5.569**	335.62	1	0	1	4	250.07	17.071	103.11
9	4.53	236.31	1	0	0	4	235.21	17.071	103.11
10	4.76	256.72	1	0	0	4	232.29	17.071	103.11

a)%ABS, percentage of absorption; **MW**, molecular weight; **HBD**, number of H-bond donors; **HBA**,number of H-bond acceptors;;**nrotb**, number of rotaTable bonds; **nVio .number of violations;TPSA**,topological polar surface area.

Table 3: Prediction of the molecular properties for chalcones and derivatives (11-20)

S.No	CLogP	M.Wt	HBA	HBD	nVio	nrotb	Volume	TPSA	%ABS
11	4.62	287.15	1	0	0	3	219.73	17.071	103.11
12	3.301	279.33	3	1	0	5	266.60	46.169	93.071
13	3.357	309.36	4	1	0	6	292.14	55.403	89.885
14	3.749	293.36	3	1	0	5	283.16	46.169	93.071
15	3.979	313.78	3	1	0	5	280.13	46.169	93.071
16	4.584	348.22	3	1	0	5	293.67	46.169	93.071
17	3.259	324.33	6	1	0	6	289.93	91.993	77.262
18	3.403	322.40	4	1	0	6	312.50	49.407	91.954
19	3.02	285.36	3	1	0	5	257.31	46.169	93.071
20	2.378	269.3	4	1	0	5	248.16	59.309	88.53

b) **%ABS,** percentage of absorption; **MW**, molecular weight; **HBD**, number of H-bond donors; **HBA**,number of H-bond acceptors;;**nrotb**, number of rotaTable bonds; **nVio .number of violations;TPSA**,topological polar surface area.

Table4: ADME properties for chalcones (1-10)

S.No	In vitro Caco-2 (nm/sec)	HIA (%)	MDCK (nm/sec)	iPPB	C_{brain}/C_{blood}
1	54.59	100	**115.20**	94.83	1.515
2	55.38	100	**33.40**	95.78	5.52
3	56.39	100	1.93	93.61	6.08
4	56.01	100	**37.93**	100	6.31
5	55.80	100	8.98	100	2.26
6	54.95	100	**48.73**	100	5.51
7	55.17	100	**54.91**	100	2.97
8	55.69	100	0.15	100	2.41
9	55.07	100	0.74	100	6.12
10	54.92	100	**54.91**	100	2.97

c) PCaco2 (nm/sec), Caco2 cell permeability in nm/sec; HIA(%), Percentage human intestinal absorption; PMDCK (nm/sec), Madin-Darby canine kidney cell permeabity in nm/sec; PPB(%), in vitro plasma protein binding (percentage); BBB(Cbrain/Cblood), in vivo Blood-Brain Barrier penetration.

Table5: ADME properties for chalcones (11-20)

S.No	In vitro Caco-2 (nm/sec)	HIA (%)	MDCK (nm/sec)	iPPB	C_{brain}/C_{blood}
11	55.05	100	0.575	100	3.38
12	27.34	95.58	12.58	91.35	0.22
13	32.41	95.64	9.66	89.92	0.063
14	28.33	95.69	5.85	90.90	0.48
15	30.51	96.08	4.08	89.15	0.62
16	33.93	96.50	0.28	91.20	1.85
17	19.15	95.85	1.53	87.20	0.012
18	36.92	95.83	0.711	91.77	0.16
19	30.55	96.40	11.41	90.79	0.08
20	31.995	95.59	**221.8**	84.07	0.027

d) PCaco2 (nm/sec), Caco2 cell permeability in nm/sec; HIA(%), Percentage human intestinal absorption; PMDCK (nm/sec), Madin-Darby canine kidney cell permeabity in nm/sec; PPB(%), in vitro plasma protein binding (percentage); BBB(Cbrain/Cblood), in vivo Blood-Brain Barrier penetration.

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***Corresponding Author:**
shaheen.pharmchem@gmail.com