In silico analysis of Juarezic acid and Avenalumic acid analogs

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Abstract
Computer-aided drug design (CADD) plays a key role in modern drug discovery. In the present in silico study, two sets of compounds were developed computationally considering the structures of juarezic acid and avenalumic acid. In the first set (compounds 1 – 8), the carboxylic acid group was replaced by ester, amide or nitrile. In the second set (compounds 9 – 16), α-nitrile substituent was introduced and verified its effect on molecular properties especially log P, hydrogen bond acceptor and TPSA as well as druglikeness, pharmacokinetics, bioactivity score and toxicity using Molinspiration Cheminformatics, SwissADME and OSIRIS Property Explorer. All the compounds were evaluated in silico and were found to obey Lipnski's rule confirming their druglikeness and pharmacokinetic properties. Among all, avenalumic acid, avenalumamide, α-cyanoavenalumic acid and juarezic acid (compounds 5, 7, 13 and 1) were estimated as active enzyme inhibitors. Additionally, α-cyanoavenalumic acid 13 was estimated as an active nuclear receptor ligand. These observations indicate the essential structural requirements like phenolic hydroxyl group, a diene system conjugating with carboxylic acid or amide and α-nitrile substitution for the bioactivity as enzyme inhibitor and nuclear receptor ligand. Most of the compounds appear to have BBB permeability and low toxicity risks. Hence, they may be synthesized and screened for their CNS activity.

Keywords: Avenalumic acid, Juarezic acid, *In silico* analysis.

Introduction

Computer-Aided Drug Design (CADD) is a powerful and interdisciplinary field that plays a pivotal role in modern drug discovery. It combines computational techniques with biological knowledge to identify and optimize potential drug candidates. This integration of diverse methodologies contributes to the versatility and effectiveness of CADD in the pharmaceutical industry.

There are various CADD methods which include molecular docking, pharmacophore modeling and QSAR method. The principles underpinning CADD methods are the utilization of computer algorithms on chemical and biological data to simulate and predict how a drug molecule will interact with its target, usually a protein or DNA sequence in the biological system. This can range from understanding the drug's molecular structure or target and predicting how the drug will bind in forecasting the pharmacological effects and potential side effects[14].

The molecular docking methods are broadly classified into Structure-Based Drug Design (SBDD) and Ligand-Based Drug Design (LBDD). SBDD requires the information on three-dimensional structure of the biological target and ligand. When the structure of the biological target is unknown, LBDD method can be used. It requires only ligand information for predicting activity depending on its similarity/dissimilarity in three dimensional chemical structures to previously known active ligands. Pharmacophore modeling is widely used to identify potential lead molecules quickly. A pharmacophore is an assembly (3D arrangement) of 'steric' and 'electronic' features of a molecule required for optimal supramolecular interaction with a specific biological target structure and to prompt/block its biological response[16].

QSAR is essentially a computerized statistical method which tries to explain the observed variance in the biological effect of certain classes of compounds as a function of molecular changes caused by the substituents[10]. Because of drastic advancement in computing power, various computational chemistry methods are now available to calculate molecular properties and generate pharmacophore hypotheses. These newer methods of CADD can be used for screening novel or known compounds in identifying hit-to-lead and lead-to-drug, based on estimated molecular properties and pharmacophoric groups[2].

Natural products play an important role as leads for new pharmaceuticals. Natural products contain diverse and complex bioactive compounds and in the drug discovery process, natural products present exclusive features compared to conventional synthetic molecules[3,5]. Avenalumic acid is a natural phenolic acid that conjugates with 4-hydroxy anthranilic acid, usually called as avenalumamide AF8, produced in response to an infection or elicitors used on oat leaves. The existence of *E* (or trans-) and *Z* (or cis-) stereoisomers of avenalumic acid was documented. It has been reported that these isomers differ markedly in molecular dimensions and physicochemical properties and they are readily interconvertible in ultraviolet light, even when covalently attached to high molecular weight compounds[4].

A non-phenolic analog of avenalumic acid, 5-phenylpenta-2,4-dienoic acid, also exists in *E* and *Z* configuration[15].

Among the possible isomers, (2*E*, 4*E*)-5-phenylpenta-2,4-dienoic acid (called as juarezic acid or cinnamalacetic acid) was reported to have anti-hemorrhagic activity[1,13]. The intensive literature review revealed antifungal activity of several cinnamal derivatives against *Alternaria alternata* by spore germination inhibition technique. Among the tested compounds, 2-(3-phenylallylidene)malononitrile has been found to possess promising antifungal activity with ED50 37 ppm[11]. Earlier, it has been reported that α-cyano-5-phenyl-2, 4-pentadienoic acid (α-cyanojuarezic acid) acts as an inhibitor of the mitochondrial pyruvate carrier[7].

Recently, the synthesis and matrix properties of α-cyanojuarezic acid for intact protein analysis by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) were demonstrated. It has been reported that α-cyanojuarezic acid exhibited better signal-to-noise ratio and a uniform response for most examined proteins occurring in milk, hazelnut and intact bacterial cells of *E. coli*[12]. A review report on several drugs and drug leads containing cyano/nitrile group revealed the efficacious roles of nitrile pharmacophore[6]. The accumulated knowledge on nitrile compounds, juarezic acid and avenalumic acid derivatives prompted us to carry out *in silico* analysis of various juarezic acid and avenalumic acid analogs with a focus on the effect of nitrile group at α position of juarezic acid and avenalumic acid derivatives.

The main aim of present study is to know the druglikeness and pharmacokinetic profile of juarezic acid and avenalumic acid analogs based on molecular properties and to estimate bioactivity, toxicity and medicinal chemistry friendliness of juarezic acid and avenalumic acid analogs using free web-based cheminformatics tools.

Material and Methods

ChemDraw is a molecule editor software program first developed in 1985. ChemDraw has many applications viz. drawing chemical structures, giving names to chemical structure, in the conversion of a chemical name to structure, structure to SMILES (Simplified Molecular Input Line Entry System) and in NMR spectrum simulation (^{1}H and ^{13}C) etc. Presently, ChemDraw Ultra 12.0.2 was used to generate sixteen chemical structures of juarezic acid and avenalumc acid analogs (1 to 16).

Molinspiration Cheminformatics is used for the prediction of various molecular properties of compounds having a valid chemical structure. The molecular properties that influence molecule biological activity, include log P, molecular weight, volume, hydrogen bond acceptor, hydrogen bond donor, number of rotatable bonds and topological polar surface area (TPSA). In addition to the estimation of above molecular properties, this computational tool is also used for the calculation of bioactivity score of the compounds as G-protein coupled receptor (GPCR) ligands, ion channel modulators, kinase inhibitors, nuclear receptor ligands, protease inhibitors and enzyme inhibitors based on Molinspiration technology.

SwissADME, a freely accessible web tool was used to compute physicochemical properties, ADME parameters, druglike nature, boavailability score and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery. SwissADME strong points are non-exhaustively different input methods, computation for multiple molecules and the possibility to display, save and share results of individual or multiple molecules through global intuitive and interactive graphs.

OSIRIS Property Explorer was used to draw chemical structures or generate structures from the SMILES notations and to calculate various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of mutagenic, tumorigenic, irritant and reproductive effects are shown in red whereas low risks of toxicity shown in green color indicate drug-confirm behaviour.

Results and Discussion

The molecular properties, bioactivity, pharmacokinetic and toxicity profile of juarezic acid and avenalumic acid analogs were estimated using free online computational tools Molinspiration Cheminformatics, SwissADME and OSIRIS Property Explorer. Initially, the molecular structure and nomenclature of sixteen different cinnamylidene compounds were generated using ChemDraw Ultra 12.0.2 and the data presented in table 1.

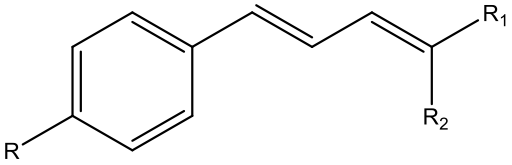
The first four compounds (1-4) were juarezic acid derivatives and next four compounds (5-8) were avenalumic acid derivatives. The carboxylic acid functional groupof juarezic acid and avenalumic acid were modified to ester, amide and nitrile groups. In another set of compounds (9-16), nitrile (cyano) group was introduced at α carbon of juarezic acid and avenalumic acid derivatives.

These compounds were considered for the present study based on the structural features of some phenolic Tyrphostins such as Tyrphostin AG 30, Tyrphostin A25, Tyrphostin AG 99, Tyrphostin AG 9, Tyrphostin AG 10 and Tyrphostin AG 112. Among the computationally selected cinnamylidene derivatives, the compounds 1 to 12 were previously existing and few of them known to possess biological activities while the compounds 13 to 16 were new and not reported previously.

The molecular properties of all the generated structures were calculated using Molinspiration Cheminformatics and the data presented in table 2. The druglikeness of all these compounds was evaluated by Lipinski's rule of five that deals with four simple physicochemical properties (log P $\leq$ 5, molecular weight $\leq$ 500, number of hydrogen bond acceptors $\leq$ 10, number of hydrogen bond donors $\leq$ 5). The log P measurement was used to understand the substance solubility behaviour and hence its oral absorption and

bioavailability. The *in silico* study revealed that the milog P values of all the juarezic acid and avenalumic acid analogs lie between 1.16 and 3.42 (within acceptable range ≤ 5).

Table 1
Nomenclature and Molecular Formula of Juarezic acid and Avenalumic acid analogs



C. No.	Nomenclature	Molecular formula	R	R_1	R_2
1	(2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid (Juarezic acid)	$C_{11}H_{10}O_2$	H	COOH	H
2	(2*E*,4*E*)-ethyl 5-phenylpenta-2,4-dienoate	$C_{13}H_{14}O_2$	H	$COOC_2H_5$	H
3	(2*E*,4*E*)-5-phenylpenta-2,4-dienamide	$C_{11}H_{11}NO$	H	$CONH_2$	H
4	(2*E*,4*E*)-5-phenylpenta-2,4-dienenitrile	$C_{11}H_9N$	H	CN	H
5	(2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienoic acid (Avenalumic acid)	$C_{11}H_{10}O_3$	OH	COOH	H
6	(2*E*,4*E*)-ethyl 5-(4-hydroxyphenyl)penta-2,4-dienoate	$C_{13}H_{14}O_3$	OH	$COOC_2H_5$	H
7	(2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienamide	$C_{11}H_{11}NO_2$	OH	$CONH_2$	H
8	(2*E*,4*E*)-5-(4-hydroxyphenyl)penta-2,4-dienenitrile	$C_{11}H_9NO$	OH	CN	H
9	(2*E*,4*E*)-2-cyano-5-phenylpenta-2,4-dienoic acid	$C_{12}H_9NO_2$	H	COOH	CN
10	(2*E*,4*E*)-ethyl 2-cyano-5-phenylpenta-2,4-dienoate	$C_{14}H_{13}NO_2$	H	$COOC_2H_5$	CN
11	(2*E*,4*E*)-2-cyano-5-phenylpenta-2,4-dienamide	$C_{12}H_{10}N_2O$	H	$CONH_2$	CN
12	(*E*)-2-(3-phenylallylidene)malononitrile	$C_{12}H_8N_2$	H	CN	CN
13	(2*E*,4*E*)-2-cyano-5-(4-hydroxy phenyl)penta-2,4-dienoic acid	$C_{12}H_9NO_3$	OH	COOH	CN
14	(2*E*,4*E*)-ethyl 2-cyano-5-(4-hydroxyphenyl)penta-2,4-dienoate	$C_{14}H_{13}NO_3$	OH	$COOC_2H_5$	CN
15	(2*E*,4*E*)-2-cyano-5-(4-hydroxyphenyl)penta-2,4-dienamide	$C_{12}H_{10}N_2O_2$	OH	$CONH_2$	CN
16	(*E*)-2-(3-(4-hydroxyphenyl) allylidene)malononitrile	$C_{12}H_8N_2O$	OH	CN	CN

Note: C.No. means compound numbers.

Table 2
Prediction of Molecular properties of Juarezic acid and Avenalumic acid analogs using Molinspiration Cheminformatics

C. No.	milogP	MW	nON	nOHNH	n violations	n rotb	Volume	TPSA	%ABS
1	2.43	174.20	2	1	0	3	165.88	37.30	96.13
2	3.42	202.25	2	0	0	5	200.21	26.30	99.92
3	1.92	173.22	2	2	0	3	169.15	43.09	94.13
4	2.97	155.20	1	0	0	2	155.74	23.79	100.79
5	1.95	190.20	3	2	0	3	173.90	57.53	89.15
6	2.94	218.25	3	1	0	5	208.23	46.53	92.94
7	1.44	189.21	3	3	0	3	177.17	63.32	86.80
8	2.49	171.20	2	1	0	2	163.75	44.02	93.81
9	2.15	199.21	3	1	0	3	182.74	61.09	87.92
10	3.14	227.26	3	0	0	5	217.07	50.10	91.71
11	1.64	198.22	3	2	0	3	186.01	66.89	85.92
12	2.69	180.21	2	0	0	2	172.60	47.58	82.58
13	1.67	215.21	4	2	0	3	190.76	81.32	80.94
14	2.67	243.26	4	1	0	5	225.09	70.33	84.73
15	1.16	214.22	4	3	0	3	194.03	87.11	78.94

(miLogP: partition coefficient, MW: Molecular weight, nON: Hydrogen bond acceptor, nOHNH: Hydrogen bond donor, n Violations: Number of violations, n rotb: Number of rotatable bonds, TPSA: Topological polar surface area, %ABS: Percentage of absorption)

The lipophilicity of compounds 1 to 8 was high when compared with the respective nitrile substituted compounds 9 to 16. The data also revealed that the lipophilicity was increased as the functional group (R_1) at 1st position changes from amide to acid, acid to nitrile and nitrile to ester. All the juarezic acid and avenalumic acid analogs have an acceptable range of molecular weight. They possess an adequate number of hydrogen bond acceptors and hydrogen bond donors. It has been observed that the introduction of α-nitrile group causes an increase in number of hydrogen bond acceptors, ensuring efficient interaction with hydrogen bonding groups of an intractable receptor.

The number of rotatable bonds explained the flexibility and conformational changes of molecules for binding to the receptors. It has been accepted that the number of rotatable bonds should be ≤ 10 to pass the oral bioavailability. The α-nitrile compounds (4, 8, 12 and 16) have two rotatable bonds and therefore exhibit restricted conformational flexibility. The carboxylic acid compounds (1, 5, 9 and 13) and amide compounds (3, 7, 11 and 15) possess three rotatable bonds and hence exhibit limited conformational flexibility. The ethyl ester compounds (2, 6, 10 and 14) consist of five rotatable bonds indicating optimum conformational flexibility.

TPSA, a very useful physicochemical parameter of molecules, gives information about the polarity of compounds. It is used to predict the transport properties of compounds such as intestinal absorption and blood brain barrier (BBB) penetration. It was observed that the TPSA values of all the predicted molecules were found between 23.79 and 87.32 $Å^2$. Using TPSA values, percentage of absorption was calculated by the formula %ABS= 109-(0.345*TPSA) and the results are presented in table 2. The data indicated that juarezic acid and avenalumic acid analogs exhibited good absorption ranging from 78.94% to 100.79%. Furthermore, all the juarezic acid and avenalumic acid analogs obey Lipinski's rule of five indicating druglikeness.

The bioactivity scores of the juarezic acid and avenalumic acid analogs were calculated by Molinspiration Cheminformatics software and the data presented in table 3. The bioactivity score gives the information about binding cascade of the molecules with different protein structures and it is used for the identification of new functional drugs with increased binding selectivity profile and less undesirable effects. It is well documented that if the bioactivity score is more than 0.00, the molecules have better biological activity. If the bioactivity score is -0.50 to 0.00, the molecules have moderate activity and if the score is beyond -0.50, the molecules have no biological activity[8]. The results of bioactivity data indicated that avenalumic acid, avenalumamide, α-cyanoavenalumic acid and juarezic acid (compounds 1, 5, 7 and 13) were active as enzyme inhibitors.

All other compounds were moderately active as enzyme inhibitors. This observation indicated the important structural components for the enzyme inhibitor activity which include cinnamylideneacetic acid or cinnamylideneacetamide, a phenolic hydroxyl group at 4th position on phenyl ring and a nitrile substitution at α carbon. Among the screened compounds, only α-cyanoavenalumic acid (compound 13) was active as nuclear receptor ligand and with few exceptions, all other compounds were moderately active as nuclear receptor ligands.

Table 3
Prediction of Bioactivity scores of Juarezic acid and Avenalumic acid analogs using Molinspiration Cheminformatics

C. No.	GPCR Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	-0.39	-0.25	-0.81	-0.35	-0.60	0.00
2	-0.53	-0.33	-0.78	-0.44	-0.57	-0.16
3	-0.51	-0.34	-0.47	-0.80	-0.66	-0.04
4	-0.80	-0. 56	-0.81	-0.89	-0.76	-0.26
5	-0.25	-0.14	-0.61	-0.05	-0.51	0.12
6	-0.37	-0.21	-0.60	-0.12	-0.46	-0.03
7	-0.34	-0.20	-0.29	-0.41	-0.53	0.10
8	-0.59	-0.39	-0.60	-0.48	-0.62	-0.09
9	-0.43	-0.22	-0.73	-0.24	-0.61	-0.04
10	-0.58	-0.37	-0.75	-0.38	-0.69	-0.28
11	-0.65	-0.52	-0.63	-0.74	-0.72	-0.27
12	-0.74	-0.44	-0.75	-0.68	-0.92	-0.33
13	-0.30	-0.13	-0.56	0.03	-0.52	0.06
14	-0.43	-0.28	-0.59	-0.10	-0.58	-0.16
15	-0.48	-0.39	-0.46	-0.40	-0.60	-0.13
16	-0.56	-0.31	-0.56	-0.33	-0.77	-0.17

The careful observation of bioactivity as nuclear receptor ligands revealed that amide and nitrile analogs of juarezic acid (compounds 3 and 4) and their α-cyano derivatives (compounds 11 and 12) were inactive.

Further, the data indicated that the introduction of nitrile substitution at α carbon of other juarezic acid and avenalumic acid analogs improved the bioactivity as nuclear receptor ligands. The bioactivity as ion channel modulator indicated that compounds 4 and 11 were inactive while other investigated compounds were moderately active. Introduction of α-nitrile substitution in acid and nitrile derivatives strengthened the ion channel modulator activity whereas in ester and amide derivatives, the activity attenuated. The predicted bioactivity data revealed moderate activity of avenalumic acid, avenalumamide, ethyl ester of avenalumic acid, α-cyanoavenalumic acid, juarezic acid, α-cyanojuarezic acid, ethyl ester of α-cyanoavenalumic acid and α-cyanoavenalumamide (compounds 5, 7, 6, 13, 1, 9, 14 and 15) as GPCR ligands.

The data also indicated moderate activity as kinase inhibitors for the amide derivatives of avenalumic acid, juarezic acid and α-cyanoavenalumic acid (compounds 7, 3 and 15). Only ethyl ester of avenalumic acid was moderately active as protease inhibitor among the screened compounds. Keen observation of bioactivity data proves the beneficial effect of phenolic hydroxyl group of avenalumic acid analogs when compared with juarezic acid analogs.

SwissADME web tool was used to estimate the pharmacokinetics, druglikeness, bioavailability score and medicinal chemistry friendliness of juarezic acid and avenalumic acid analogs. The data presented in table 4 and table 5. The observation of data indicated that the juarezic acid and avenalumic acid analogs have high gastrointestinal absorption. Except compound 13 and 15, all the compounds have BBB permeation as their TPSA values were less than 78.00 $Å^2$ and have an optimum lipophilicity. All the juarezic acid and avenalumic acid analogs were identified as non-substrates of permeability glycoprotein (P-gp) and as non-inhibitors of CYP2C9, CYP2D6 and CYP3A4.

Among the series, compounds 1, 2, 3, 5, 6, 7, 9 and 13 were non-inhibitors of CYP1A2, while other compounds were inhibitors. Only the compounds having ethyl ester group (2, 6, 10 and 14) were inhibitors of CYP2C19. The estimated Log Kp values of all the compounds were in the range of -4.88 to -6.58. The highly polar groups of the compounds contribute to the more negative Log K_p, indicating less skin permeation.

In the present investigation, juarezic acid and avenalumic acid analogs were analyzed for the druglikeness by five different rule-based filters Lipinski, Ghosh, Veber, Egan and Muegge. The data indicated that the compounds having molecular weight less than 200 and 160 violated Muegge and Ghosh methods respectively. The calculated bioavailability score of juarezic acid, avenalumic acid and α-cyanojuarezic acid was 0.85 indicating the probability of 85% oral bioavailability. The estimated bioavailability score of α-cyanoavenalumic acid (compound 13) was 0.56 whereas the bioavailability score of all other compounds was 0.55 indicating the probability of 56% and 55% oral bioavailability respectively.

Table 4
Prediction of Pharmacokinetics of Juarezic acid and Avenalumic acid analogs using SwissADME

C.No.	GI absorption	BBB permeant	P-gp substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log Kp
1	High	Yes	No	No	No	No	No	No	-5.13
2	High	Yes	No	No	Yes	No	No	No	-4.96
3	High	Yes	No	No	No	No	No	No	-5.58
4	High	Yes	No	Yes	No	No	No	No	-4.88
5	High	Yes	No	No	No	No	No	No	-5.48
6	High	Yes	No	No	Yes	No	No	No	-5.60
7	High	Yes	No	No	No	No	No	No	-6.38
8	High	Yes	No	Yes	No	No	No	No	-5.68
9	High	Yes	No	No	No	No	No	No	-5.78
10	High	Yes	No	Yes	Yes	No	No	No	-5.51
11	High	Yes	No	Yes	No	No	No	No	-5.95
12	High	Yes	No	Yes	No	No	No	No	-5.40
13	High	No	No	No	No	No	No	No	-6.13
14	High	Yes	No	Yes	Yes	No	No	No	-5.85
15	High	No	No	Yes	No	No	No	No	-6.58
16	High	Yes	No	Yes	No	No	No	No	-5.88

Table 5
Prediction of Druglikeness, Bioavailability, Toxicity, Lead-likeness and Syntheticaccessibility of Juarezicacid and Avenalumic acid analogs using SwissADME

C.No.	Druglikeness	Bioavailability Score	Toxicity P/B	Lead-likeness	Synthetic accessibility
1	Yes*	0.85	0/2	No	2.52
2	Yes	0.55	0/2	No	2.86
3	Yes*	0.55	0/2	No	2.45
4	Yes**	0.55	0/2	No	2.73
5	Yes*	0.85	0/2	No	2.37
6	Yes	0.55	0/2	No	2.74
7	Yes*	0.55	0/2	No	2.28
8	Yes*	0.55	0/2	No	2.45
9	Yes*	0.85	0/3	No	2.69
10	Yes	0.55	0/3	No	3.02
11	Yes*	0.55	0/3	No	2.63
12	Yes*	0.55	0/2	No	2.67
13	Yes	0.56	0/3	No	2.56
14	Yes	0.55	0/3	No	2.92
15	Yes	0.55	0/3	No	2.48
16	Yes*	0.55	0/2	No	2.43

Note:
***** Violation of Muegge rule: MW < 200
****** Violation of Ghose rule: MW < 160 and violation of Muegge rule: MW < 200, heteroatom< 2

Table 6
Drug-relevant properties, toxicity risks, drug-likeness and drug score of Juarezic acid and Avenalumic acid analogs using Osiris Property Explorer

C.No.	cLogP	Log S	MW	TPSA	Toxicity Risks				DL	DS
					M	T	I	R		
1	2.13	-2.31	174.20	37.30	Nil	Nil	High	Nil	-4.52	0.28
2	2.96	-2.74	202.25	26.30	Nil	Nil	High	Nil	-12.92	0.27
3	1.73	-2.39	173.22	43.09	Nil	Nil	High	Nil	-5.86	0.28
4	2.65	-2.98	155.20	23.79	Nil	Nil	High	Nil	-10.34	0.27
5	1.78	-2.02	190.20	57.53	Nil	Nil	Nil	Nil	0.82	0.80
6	2.62	-2.44	218.25	46.53	Nil	Nil	Nil	Nil	-7.48	0.45
7	1.39	-2.09	189.21	64.32	Nil	Nil	Nil	Nil	-0.47	0.66
8	2.31	-2.69	171.20	44.02	Nil	Nil	Nil	Nil	-4.8	0.46
9	1.98	-2.58	199.21	61.09	Nil	Nil	High	Nil	-6.56	0.28
10	2.82	-3.01	227.26	50.10	Nil	Nil	High	Nil	-10.28	0.26
11	1.58	-2.66	198.22	66.89	Nil	Nil	High	Medium	-5.94	0.22
12	2.5	-3.26	180.21	47.58	Nil	Nil	High	Nil	-11.8	0.26
13	1.64	-2.29	215.21	81.32	Nil	Nil	Nil	Nil	-3.18	0.49
14	2.47	-2.71	243.26	70.33	Nil	Nil	High	Nil	-6.84	0.27
15	1.24	-2.36	214.22	87.11	Nil	Nil	Nil	Medium	-2.54	0.40
16	2.16	-2.96	196.21	67.81	Nil	Nil	Nil	Nil	-8.27	0.45

(cLogP: Logarithm of Partition-Coefficient; Log S: Solubility; MW: Molecular Weight; TPSA: Total Polar Surface Area; M: Mutagenic; T: Tumorigenic; I: Irritant; R: Reproductive effect; DL: Drug Likeness; DS: Drug Score)

SwissADME was also used to estimate medicinal chemistry friendliness aspects like identification of potentially problematic fragments, lead-likeness and synthetic accessibility of compounds. The potentially problematic fragments are indicated by PAINS (Pan Assay Interference Compounds) and Brenk alerts[9]. According to the PAINS method, all the compounds were predicted as non-toxic and the Brenk method indicated the Michael acceptor, polyene and conjugated nitrile groups as problematic fragments. Usually, SwissADME assess lead-likeness by applying PAINS and Brenk filters along with other physicochemical filters. All the compounds of present study appeared to have no lead-likeness.

The synthetic accessibility of compounds was estimated, based on the historical synthetic knowledge obtained by analyzing information from millions of already synthesized chemicals, by considering molecular complexity and fragment contribution. The ease of synthesis is generally scored from 1 to 10. As the score increases, the synthesis will become very difficult. The synthetic accessibility score of all the evaluated compounds appeared between 2.28 and 3.02, indicating that they can be easily prepared by following appropriate synthetic routes.

The toxicity risks of Juarezic acid and Avenalumic acid analogs were assessed using OSIRIS property explorer. The molecular properties such as cLogP, solubility, molecular weight, TPSA as well as drug likeness and drug score were also estimated and the data presented in table 6. The study revealed that the avenalumic acid analogs (compounds 5 – 8) were predicted as safe and non-toxic. These compounds were predicted with better drug score ranging from 0.80 to 0.45. Modification of the carboxylic acid group of avenalumic acid to amide, nitrile and ester groups resulted in reduced drug score. The estimated data indicated that the juarezic acid analogs (compounds 1 – 4) have an irritant effect and the drug score was between 0.28 and 0.27.

The variation in drug score of juarezic acid and avenalumic acid anlogs is mainly due to the phenolic hydroxyl group. Introduction of nitrile substituent on α carbon atom of juarezic acid analogs, as in compounds 9 to 12, slightly altered toxicity risks and drug score. Among all, the amide derivative (compound 11) has the least drug score. The introduction of nitrile substituent on α carbon atom of avenalumic acid analogs, as in compounds 13 to 16, leads to reduced drug score that is apparently higher than the drug score of compounds 9 to 12. This observation further indicated the importance of phenolic hydroxyl group especially in acid, nitrile and amide compounds. Among the compounds 13 to 16, the acid and nitrile derivatives were non-toxic.

Conclusion

Computer-aided drug design (CADD), a modern approach to drug development, utilizes a wide variety of theoretical and computational techniques. Cheminformatics is considered as one of the CADD methods dealing with the design, analysis, management and visualization of small molecules data for the drug discovery process. Most of the time, natural products play a distinct role as leads for the development of new drug candidates. Therefore, in the present study, two sets of compounds were developed computationally considering the structures of natural products, juarezic acid and avenalumic acid. In the first set (compounds 1 to 8) carboxylic acid group of juarezic acid and avenalumic acid was modified into its derivatives like ester, amide and nitrile groups.

In the second set (compounds 9 to 16), α-nitrile substituent was introduced into the first set compounds based on the observation of medicinal properties of nitrile containing pharmaceuticals. Among the computationally developed compounds, the α-cyanoavenalumic acid derivatives (compounds 13 to 16) were new and not reported earlier. The molecular properties, druglikeness, bioactivity score, pharmacokinetics, bioavailability score, toxicity risks and medicinal chemistry friendliness aspects such as leadlikeness and synthetic accessibility of all the compounds were estimated using Moinspiration Cheminformatics, SwissADME and OSIRIS Property Explorer. All the compounds were predicted to have druglikeness properties and good pharmacokinetic profile. The bioactivity data revealed that avenalumic acid, avenalumamide, α-cyanoavenalumic acid and juarezic acid (compounds 1, 5, 7 and 13) were active as enzyme inhibitors.

Among all the compounds, the new α-cyanoavenalumic acid 13 was estimated as an active nuclear receptor ligand. These observations indicate the essential structural requirements like phenolic hydroxyl group, a diene system conjugating with carboxylic acid or amide and α-nitrile substitution for the bioactivity as enzyme inhibitor and nuclear receptor ligand. All the compounds were estimated to have a low synthetic accessibility score. Therefore, they can be synthesized by following the appropriate synthetic route, hopefully the novel 4-hydroxy cinnamylidene derivatives. Further, most of the compounds appear to have BBB permeability and low toxicity. Hence, they may be screened for their CNS activity.

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