Drug Development of Kenyan Herbal Medicine: In Silico Evaluation and Prediction of Novel Derivatives of Polygonum Senegalense Chalcone Extracts as Anti-Cancer Agents

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https://doi.org/10.62049/jkncu.v6i2.599

Abstract

Chalcones are versatile, reactive α, β-unsaturated -unsaturated cyclic aromatic molecules that can be synthetically modified and optimized into drug-like molecules. In the present study, in silico cytotoxicity prediction, Physicochemical, Pharmacokinetic, ADME (Absorption, Distribution, Metabolism, and Excretion), and Medicinal Chemistry evaluation analyses were carried out on heterocyclic derivatives of Polygonum senegalense chalcones. Cell line cytotoxicity prediction based on Prediction of Activity Spectra for Substances (PASS) technology was performed, and the training set was created based on cytotoxicity data retrieved from the Chemical Database of Bioactive Molecules (ChEMBLdb). In addition, estimation of absorption, distribution, metabolism, and excretion (ADME) using physicochemical, drug-likeness, pharmacokinetics, and medicinal chemistry properties was carried out. The highest cytotoxicity of the molecules revealed Pa values of about 0.7 in targeted cancer cell lines that included ovarian adenocarcinoma, breast carcinoma, renal carcinoma, and glioblastoma, underscoring the therapeutic potential of chalcones in our library. The data revealed that most of the compounds obey Lipinski's rule of five, may be absorbed by the gastrointestinal (GI)tract, may not penetrate the blood-brain barrier, and possess drug-like properties. This research data informs both the scientific and non-scientific communities with vital strategies for early drug development.

Keywords: Chalcones, Cytotoxicity, ADME, Druglikeness, Pharmacokinetics

Background

A potent molecule is considered an effective drug only when it can reach its target in the body in sufficient concentration and remain in its bioactive form to cause the expected medical outcome.[1]. The common method to assess pharmacokinetics (i.e., the fate of a therapeutic compound in the organism) is to break down the various effects that impact access to the target into individual parameters, namely absorption, distribution, metabolism, and excretion (ADME).

The drug discovery and development process is generally rigorous and time- and resource-consuming. The process involves assessment of absorption, distribution, metabolism, and excretion (ADME) in the early clinical trials to select molecules with the best chance of becoming an effective drug for the patients. However, the process can be made easier, faster, and more visible by the application of computer models. It significantly reduces the fraction of pharmacokinetics-related failure in the clinical phases[3]. These models provide a valid alternative to experimental procedures for prediction of ADME, especially at initial steps, when investigated chemical structures are numerous, but the availability of compounds is scarce[2]. In the present study, the SwissADME web tool was employed because it is a fast yet robust predictive model for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness [1]. Since in vivo ADME assessment is proven to be expensive, time-consuming, and involving animal studies, in-vitro ADME analysis was preferred because it was less expensive and gave accurate data more rapidly[4].

Molecules can also be directly described by substructure searches as compared to physicochemical parameters that give a global description of the structure. These techniques are at the root of Structural Alert [Ruth Brek] 5, the PAINS[5] or the Lilly MedChem7 filters applied to cleanse chemical libraries from compounds most likely unstable, reactive, toxic, or prone to interfere with biological assays because of nonspecific frequent hitters, dyes, or aggregators[6].

A large variety of *in silico* methods share the objective of predicting ADME parameters from molecular structure.[6]. Notably, the pioneering work of Lipinski et al. examined orally active compounds to define physicochemical ranges for high probability of being an oral drug (i.e., the drug-likeness) LIPINSKI. The so-called Rule of Five delineated the relationship between pharmacokinetic and physicochemical parameters.[4]. The use of substructural alerts to identify Pan-Assay Interference Compounds (PAINS) has become a common component of the triage process in biological screening campaigns.[7].

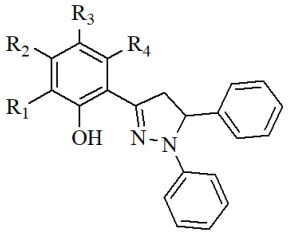
In the present study, heterocyclic analogues, previously derived from *P. senegalense* chalcones, were subjected to in Silico evaluation and prediction as anti-cancer candidates for anticancer potency. The synthesized compounds were evaluated for their physicochemical properties and pharmacokinetic profile through SwissADME.

The plant is rich in chalcones (1,3-diphenyl-2-propen-1-ones) that are embedded in its surface exudates.[8,9]. The compounds, though significantly found in plants, can be easily synthesized in the laboratories.[10]. They are versatile, active lead molecules for the discovery of new drugs.[11]. Subsequently, they have been identified as good starting materials for the synthesis of several cyclic compounds with broad spectra of biological activities.[12,13].

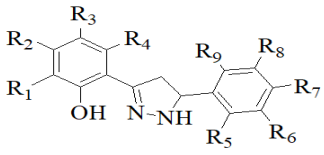
Some of the compounds under investigation in this study have the pyrazole moiety. Previous evaluations by different groups indicate that compounds with this type of structural pattern have anti-cancer properties.[14–16]. Pyrazoline ring-containing systems have also been detected as being anti-proliferative[16–21]. Similarly, heterocycles with vicinal nitrogen and oxygen, as in the case of isoxazoline, isoxazole and oxazole, have also demonstrated anti-cancer effects[9–11]. Pyrimidine derivatives, though their heteroatomic nitrogen is in a 1,3-position relationship in a six-membered ring system, have also exerted anticancer potential through different action mechanisms[22–25]. Nitrogen-containing acyclic and heterocyclic imines, enamines, and oximes have been targets of investigation for anti-cancer activity and have been found to have potent inhibitory activity.[26–28].

Materials and Methods

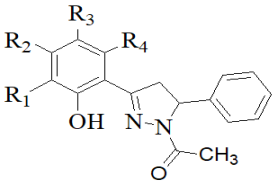
Materials Used in This Study Are Synthetic Analogues Derived from Chalcones Previously Isolated from P. senegalense[8].



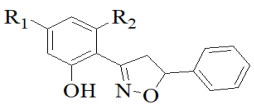
Compound	R_1	R_2	R_3	R_4
1	H	OMe	H	OMe
2	H	OMe	OH	OMe
3	H	OH	H	OMe
4	OMe	H	OMe	OH



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
5	H	OMe	OH	OMe	H	H	H	H
6	H	OMe	H	OMe	H	H	H	H
7	H	OH	H	OMe	H	H	H	H
8	H	OMe	H	OMe	OMe	OMe	OMe	OMe



Compound	R_1	R_2	R_3	R_4
9	H	OMe	OH	OMe
10	H	OMe	H	OMe



Compound	R_1	R_2
11	OMe	OMe
12	OH	OMe

Figure 1: Derivatives of P. Sengalence Chalcones

In Silico Anti-Cancer Analyses

We performed Cell line cytotoxicity prediction based on PASS (Prediction of Activity Spectra for Substances) technology (http://www.way2drug.com/PASSonline) and the training set created based on data on cytotoxicity retrieved from ChEMBLdb (version 23) (https://www.ebi.ac.uk/chembldb/). We used SMILES to input structures of the chalcones to perform cytotoxicity prediction using CLC-Pred.

CLC-Pred (Cell Line Cytotoxicity Predictor) is a web service for in silico prediction of the cytotoxic effect of chemical compounds in non-transformed and cancer cell lines based on the structural formula. CLC-Pred provides a prediction of the cytotoxicity of a chemical compound to assess the relevance of the substance's inclusion in experimental screening.

SIB website http://www.swissadme.ch was also accessed in a web browser that displays the submission page of SwissADME. The above molecules (1-12) were input for estimation of ADME, physicochemical, drug-likeness, pharmacokinetics, and medicinal chemistry properties. The input zone comprises a molecular sketcher based on ChemAxon's Marvin JS (http://www.chemaxon.com) that allows the user to draw and edit 2D chemical structures. The structures are transferred as a list to the right-hand side of the submission page, which is the actual input for computation. The list is made to contain one input molecule per line, defined by the simplified molecular-input line-entry system (SMILES), and results are presented for each molecule in tables, graphically, and as an Excel spreadsheet.

Results and Discussion

In Silico Cytotoxicity Prediction

We performed in silico cytotoxicity prediction using the CLC prediction tool. The highest cytotoxicity of the molecules revealed Pa values of more than 0.6 with targeted cell lines that include ovarian adenocarcinoma, breast carcinoma, renal carcinoma, and glioblastoma (Table 1). The predicted activity spectrum in PASS is represented by a list of activities with probabilities «to be active» Pa and «to be inactive» Pi. The list of predicted activities is arranged in descending order according to Pa–Pi values.[1]. Thus, the more probable activity types are at the top of the list, as shown in Table 1. Of note are compounds 11 and 12, the two most cytotoxic chalcones from our library, with Pa values of 0.747, respectively, that have specificity for ovarian adenocarcinoma. Previously, the application of virtual screening of libraries of commercially available compounds allowed the selection of lead compounds confirmed to have biological activity in breast cancer cells.[2]. Biological evaluation of 49 selected compounds against MDA-MB-231 and MCF7 breast cancer cell lines confirmed the activity of 8 compounds with IC_{50} values below 50 µM[2]. Thus, *in silico* cytotoxicity prediction may be applied for virtual screening of cytotoxic compounds with high correlation with biological activity against cancer cell lines.

Table 1: Cytotoxicity from CLC pred prediction

Compound	Pa	Pi	Cell-Line	Cell-Line Name	Tissue/Organ
1	0.722	0.017	MCF7	Breast carcinoma	Breast
2	0.679	0.022	MCF7	Breast carcinoma	Breast
3	0.727	0.017	MCF7	Breast carcinoma	Breast
4	0.705	0.019	MCF7	Breast carcinoma	Breast
5	0.689	0.006	RXF 393	Renal carcinoma	Kidney
6	0.694	0.006	RXF 393	Renal carcinoma	Kidney
7	0.693	0.006	RXF 393	Renal carcinoma	Kidney
8	0.736	0.005	SNB-75	Glioblastoma	Nervous system
9	0.639	0.008	RXF 393	Renal carcinoma	Kidney

10	0.642	0.008	RXF 393	Renal carcinoma	Kidney
11	0.747	0.005	OVCAR-8	Ovarian adenocarcinoma	Ovarium
12	0.747	0.005	OVCAR-8	Ovarian adenocarcinoma	Ovarium

In silico Physicochemical, Pharmacokinetic, ADME, and Medicinal Chemistry Evaluation

Physicochemical Properties of Compounds

Molecular and physicochemical properties—such as molecular weight (MW), molecular refractivity (MR), specific atom counts, and topological polar surface area (TPSA)—are critical in drug design. The optimal ranges for these properties are defined as: size with molecular weight between 150–500 g/mol, polarity with TPSA ranging from 20–130 Å², solubility with log S ≤ 6, saturation with fraction of sp^3 carbons ≥ 0.25, and flexibility ≤ 9 rotatable bonds. Evaluation of these criteria revealed that the synthesized chalcones fell within the optimal range for the majority of these properties. For instance, MW values ranged from 285.29 g/mol for our most potent compound (12) to 404.41 g/mol for compound 8. Furthermore, all compounds possessed fewer than 9 rotatable bonds, and TPSA values remained strictly within the 20 to 130 Å² threshold. Notably, several molecules exhibited a fraction of Csp^3 below 0.25, which is characteristic of the inherently conjugated and aromatic scaffold of chalcone derivatives

Table 2: Physicochemical Properties of compounds

Molecule	Mw	#Heavy Atoms	#Aromatic Heavy Atoms	Fraction Csp3	#Rotatable Bonds	#H-Bond Acceptors	#H-Bond Donors	MR	TPSA
1	374.43	28	18	0.17	5	4	1	117.27	54.29
2	390.43	29	18	0.17	5	5	2	119.29	74.52
3	360.41	27	18	0.14	4	4	2	112.8	65.29
4	390.43	29	18	0.17	5	5	2	119.29	74.52
5	314.34	23	12	0.24	4	5	3	94.15	83.31
6	298.34	22	12	0.24	4	4	2	92.13	63.08
7	284.31	21	12	0.19	3	4	2	88.31	65.29
8	404.41	29	12	0.35	7	8	3	113.63	111
9	356.37	26	12	0.26	5	6	2	104.06	91.59
10	340.37	25	12	0.26	5	5	1	102.04	71.36
11	299.32	22	12	0.24	4	5	1	86.5	60.28
12	285.29	21	12	0.19	3	5	2	82.03	71.28

Lipophilicity Properties

Lipophilicity in drug design is generally defined as the 1-octanol/water partition coefficient (log $P_{o/w}$). One Lipophilicity criterion used to estimate optimal oral bioavailability is an $XlogP_3$ value between −0.7 and +5.0. In addition, other distinct computational measures of Lipophilicity listed in Table 3 are typically utilized to calculate a consensus log P, providing a more robust and accurate predictive estimation. The consensus (log $P_{o/w}$) is the arithmetic mean of the values predicted by five independent methods. Notably, the Lipophilicity values of all chalcones in our library fell within the optimal limits required for a bioavailable drug.

Table 3: Lipophilicity Properties

Molecule	IlogP	XlogP3	WlogP	MlogP	Silicos-IT Log P	Consensus Log P
1	3.05	4.61	3.68	3.14	4.26	3.75
2	2.76	4.25	3.38	2.6	3.78	3.35
3	2.31	4.28	3.38	2.93	3.73	3.32
4	3.25	4.25	3.38	2.6	3.78	3.45
5	2.16	2.56	1.47	1.2	2.79	2.03
6	2.29	2.91	1.76	1.75	3.27	2.4
7	1.81	2.75	1.96	1.77	2.59	2.18
8	2.98	2.47	1.49	0.34	2.97	2.05
9	2.67	1.93	1.73	1.2	2.65	2.03
10	2.82	2.29	2.02	1.73	3.13	2.4
11	2.43	2.64	2.22	1.75	3.59	2.53
12	1.84	2.57	2.27	1.5	3.07	2.25

Hydrophilicity Properties of Compounds

In drug design, water solubility may be defined as the decimal logarithm of the molar solubility in water (log S). The water solubility of a drug determines its bioavailability and gastrointestinal absorption, which are important considerations in drug development. Fortunately, all the chalcones in our library were either soluble or moderately soluble in water, with high prediction of GI absorption using the ESOL (Estimated Aqueous Solubility) model. The model was originally designed from a set of 2874 measured solubilities using linear regression against nine molecular properties. These properties included calculated $logP_{(octanol)}$, followed by molecular weight, proportion of heavy atoms in aromatic systems, and number of rotatable bonds.

Table 4: Hydrophilicity Properties of compounds

Molecule	ESOL Log S	ESOL solubility (mg/ml)	ESOL solubility (mol/l)	ESOL class	GI Absorption
1	-5.21	2.30x10-3	6.14x10-6	Moderately soluble	High
2	-5.07	3.34E-03	8.56E-06	Moderately soluble	High
3	-5.00	3.60E-03	9.99E-06	Moderately soluble	High
4	-5.07	3.34x10-3	8.56x10-6	Moderately soluble	High
5	-3.52	9.41x10-2	2.99x10-4	Soluble	High
6	-3.66	6.49x10-2	2.17x10-4	Soluble	High
7	-3.56	7.83x10-2	2.75x10-4	Soluble	High
8	-3.75	7.23E-02	1.79E-04	Soluble	High
9	-3.28	1.88x10-1	5.29x10-4	Soluble	High
10	-3.42	1.3x10-1	3.82x10-4	Soluble	High
11	-3.5	9.50E-02	3.17E-04	Soluble	High
12	-3.45	1.01E-01	3.53E-04	Soluble	High

Pharmacokinetic Properties of Compounds

The cytochrome P450 (CYP) superfamily comprises critical enzymes responsible for Phase I drug metabolism and biotransformation. The majority of clinical therapeutics are metabolized by five major CYP isoforms: CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. In vitro inhibition of these specific isoforms presents a significant risk for clinical drug-drug interactions (DDIs), which can impair metabolic clearance and induce systemic toxicities. Our most potent lead compound, molecule 12, demonstrated a highly favorable safety profile, showing no cross-inhibition against any tested CYP enzymes (Table 5). While several chalcone derivatives (compounds 1–4) exhibited pan-inhibitory activity across multiple isoforms, notable exceptions were observed. Specifically, compound 9 remained entirely devoid of CYP interaction, and compound 10 demonstrated selective inhibition restricted to CYP2C9, highlighting key structural features that mitigate off-target enzyme liabilities within this chemical series.

Table 5: Pharmacokinetic Properties of Compounds

Molecule	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
1	No	Yes	Yes	Yes	Yes
2	No	Yes	Yes	Yes	Yes
3	No	Yes	Yes	Yes	Yes
4	No	Yes	Yes	Yes	Yes
5	Yes	No	No	Yes	No
6	Yes	Yes	No	Yes	Yes
7	Yes	No	No	Yes	No
8	No	No	No	No	Yes
9	No	No	No	No	No
10	No	No	Yes	No	No
11	No	Yes	No	Yes	No
12	No	No	No	No	No

Drug-Likeness of the Molecules

To predict the oral bioavailability of the chalcone library, a qualitative drug-likeness assessment was performed using SwissADME. The molecules were screened against five established pharmaceutical filters: Lipinski, Ghose, Veber, Egan, and Muegge. These filters evaluate critical physicochemical properties including molecular weight (MW), lipophilicity (\(\log P\)), topological polar surface area (TPSA), and rotatable bond count. Remarkably, all twelve chalcone molecules exhibited zero violations across all five models (Table 6). This strict compliance indicates optimal structural and physicochemical properties, suggesting high potential for favorable oral absorption and systemic bioavailability.

Table 6: Drug-likeness of the Molecules

Molecule	Lipinski #Violations	Ghose #Violations	Veber #Violations	Egan #Violations	Muegge #Violations
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
8	0	0	0	0	0
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0

Medicinal Chemistry of the Molecules

Success in early drug discovery is dependent upon the elimination of biologically problematic molecules. This includes the removal of molecules with multiple biological targets that lead to toxicity. PAINS (for pan-assay interference compounds) are molecules containing substructures showing potent response in assays irrespective of the protein target. SwissADME evaluation alerts users when PAINS substructures are identified in the molecule. In addition, SwissADME posts alerts known as Brenk alerts on molecules with putatively toxic, chemically reactive, metabolically unstable, and pharmacokinetically poor substructures. Importantly, elimination of the potentially toxic substructures improves the chances of hitting a lead molecule. By definition, lead molecules are subjected to chemical modifications that will most likely increase size and lipophilicity. SwissADME posts leadlikeness alerts for molecules that are unlikely to undergo such modifications, thus enhancing the medicinal chemists' ability to synthesize lead molecules. While an SA score <4 is indeed excellent (indicating synthetic ease), the scoring range in SwissADME is mathematically 1 to 10.

Evaluation of SwissADME revealed that our most potent chalcones, 11 and 12, are non-toxic, have potential to be lead molecules, and do not possess unwanted substructures. In addition, the synthetic accessibility score is below 4, implying ease of synthesis that provides a viable path to further drug development. Other chalcones had either one or two violations on the SwissADME medicinal chemistry evaluation (Table 7), which ideally could be eliminated by minimal structure modification.

Table 7: Medicinal Chemistry of the Molecules

Molecule	Pains #Alerts	Brenk #Alerts	Leadlikeness #Violations	Synthetic Accessibility
1	1	0	2	3.77
2	1	1	2	3.87
3	2	0	2	3.66
4	1	0	2	3.85
5	1	1	0	3.58

6	1	0	0	3.49
7	2	0	0	2.78
8	1	0	1	4.03
9	1	1	1	3.7
10	1	0	0	3.61
11	0	0	0	3.83
12	0	0	0	3.61

Physicochemical Properties of the Compounds

Molecular and physicochemical properties like molecular weight (MW), molecular refractivity (MR), count of specific atom types, and Polar Surface Area (PSA) are critical in drug design. The optimal range for each physicochemical property is as follows: size with MW between 150 and 500 g/mol, polarity with TPSA between 20 and 130Å^2, solubility with a log S not higher than 6, saturation with a fraction of carbons in the sp^3 hybridization not less than 0.25, and flexibility with not more than 9 rotatable bonds. Evaluation of these criteria revealed that the compounds in our library were within the range for most of the physicochemical properties. For example, the MW was between 285 for our most potent molecule, compound **1**, and about 404 for compound 10. The rotatable bonds were less than 9 for all the molecules, and the TPSA was within the 20 and 130Å^2 range

Table 8: In silico Protein Target Prediction using Swiss Target Prediction

Compound	Target	Common Name	Uniprot Id	Chembl Id	Target Class	Probability*	Known Actives (3d/2d)
1	Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279	Kinase	0.197714623	575 / 9Â Â Â Â Â
2	Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase	0.157071963	132 / 101Â Â Â Â Â
3	Receptor protein-tyrosine kinase erbB-2	ERBB2	P04626	CHEMBL1824	Kinase	0.289266093	63 / 35Â Â Â Â Â
4	Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase	0.13952343	130 / 101Â Â Â Â Â
5	Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase	0.126610169	253 / 76Â Â Â Â Â
6	Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase	0.158886034	387 / 77Â Â Â Â Â
7	Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase	0.130791955	355 / 33Â Â Â Â Â
8	Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase	0	30 / 96Â Â Â Â Â
9	Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase	0.23917305	183 / 103Â Â Â Â Â
10	Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase	0.532477952	220 / 104Â Â Â Â Â
11	Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687	Enzyme	0.111501865	6 / 0Â Â Â Â Â
12	Hepatocyte growth factor receptor	MET	P08581	CHEMBL3717	Kinase	0.097874534	475 / 0Â Â Â Â Â

In silico Protein Target Prediction using Swiss Target Prediction

Bioactive small molecules bind to proteins or other macromolecular targets to modulate their activity, which in turn results in the therapeutic effects. For this reason, mapping the protein targets of bioactive small molecules is a key step toward unraveling the molecular mechanisms of the therapeutic agent. We used SwissTargetPrediction to estimate the most probable targets of the chalcones, assumed to be bioactive (Table 8)

Table 9: Protein Targets of the compounds

Molecule	Target	Common Name	Uniprot ID	Chembl ID
1	Vascular endothelial growth factor receptor 2	KDR	P35968	CHEMBL279
2	Monoamine oxidase A	MAOA	P21397	CHEMBL1951
3	Receptor protein-tyrosine kinase erbB-2	ERBB2	P04626	CHEMBL1824
4	Monoamine oxidase A	MAOA	P21397	CHEMBL1951
5	Monoamine oxidase B	MAOB	P27338	CHEMBL2039
6	Monoamine oxidase B	MAOB	P27338	CHEMBL2039
7	Monoamine oxidase B	MAOB	P27338	CHEMBL2039
8	Monoamine oxidase A	MAOA	P21397	CHEMBL1951
9	Monoamine oxidase A	MAOA	P21397	CHEMBL1951
10	Monoamine oxidase A	MAOA	P21397	CHEMBL1951
11	Arachidonate 12-lipoxygenase	ALOX12	P18054	CHEMBL3687
12	Hepatocyte growth factor receptor	MET	P08581	CHEMBL3717

Abbreviations

ADME - Absorption, Distribution, Metabolism, And Excretion)
PASS - Prediction Of Activity Spectra for Substances Technology
Chembldb - Chemical Database of Bioactive Molecules
SMILES - Simplified Molecular-Input Line-Entry System
PAIN - Pan-Assay Interference Compounds (PAINS)

Conclusion

Polygonum senegalense is very rich in chalcones (1,3-diphenyl-2-propen-1-ones) that can be derivatised to molecules with therapeutic potential. In this regard, we derivatised various chalcones to generate a library of 12 small molecules. We performed cell line cytotoxicity prediction using CLC-Pred based on PASS technology, which revealed high cytotoxicity of the molecules in various cell lines that include ovarian adenocarcinoma, breast carcinoma, renal carcinoma, and glioblastoma. Of note are the two most potent molecules, 11 and 12, with Pa values of about 0.747 and Pi values of 0.005, with drug-like physicochemical properties. These two chalcones did not have any PAINS or Brenk alerts, suggesting that they are non-toxic and may not have multiple targets. Importantly, the hydrophilicity of our chalcones is high, making these molecules bioavailable with favorable ADME and pharmacokinetic features. In addition, all our chalcones obey the Lipinski, Veber, Egan, Ghose, and Muegge rules, making them of interest to leading pharmaceutical companies. This interest is probably validated by the lead-like nature of our molecules that have low synthetic accessibility with SA scores less than 4. Encouraged by the CLC-Pred cytotoxicity and SwissADME data, we employed Swiss Target Prediction for initial protein target screening that revealed putative targets. One interesting target of our most potent chalcone, compound **1**, was Hepatocyte growth factor receptor, which has been associated with Ovarian adenocarcinoma. Interestingly, our CLC-Pred evaluation revealed that compound **1** was cytotoxic against ovarian interesting to see how the biological evaluation of our chalcones compares with *in silico* data. In this regard, we plan to send our molecules for NCI 60 screening at the National Cancer Institute-USA for screening in 60 different cancer cell lines.

Acknowledgement

the authors wish to acknowledge Swiss Institute of Bioinformatics for developing that has assisted scientists worldwide to SwissADME, a user-friendly tool for predicting drug-likeness and ADMET

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