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Virtual Screening of Molecular Properties and Bioactivity Score of Boswellic Acid Derivatives in Search of Potent Anti-Inflammatory Lead Molecule

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Abstract

The aim of this study was to examine correlation between anti-inflammatory activity and molecular properties of the Boswellic acid derivatives in search of a lead compound through molinspiration cheminformatics software. Twelve naturally occurring and semisynthetic derivatives of Boswellic acid were selected for bioactivity prediction and drug likeness score on the basis of Lipinski's rule. Aceclofenac and Hydrocortisone (cortisol) were used as reference standard for comparing the molecular properties and bioactivity score. None of the compounds fulfilled Lipinski's rule as their Molog P score was above 5 suggesting these compounds are highly lipophilic with very poor aqueous solubility. All the screened compounds had minimum one and maximum three violations of Lipinski rule. BA and its derivatives showed good bioactivity score for drug targets including nuclear receptor ligand, protease inhibitor and enzyme inhibition and thus expected to have excellent pharmacological activity in vivo. The results of this study justify their topical application in arthritic conditions but some structural modifications in order to make the compound more polar will definitely improve oral bioavailability and thus the usefulness and therapeutic efficacy of BAs. Among all the boswellic acid derivatives, only compound number 2 is predicted to be orally active and is considered as a potential candidate for the further research as its bioactivity score due to high affinity for various drug targets was better than the standard (Cortisol and Aceclofenac) as well as among other tested compounds.

Keywords : Boswellic acid, Anti-inflammatory activity, Lipinski's rule, Molinspiration

Introduction

Lead compounds possess desired pharmacological properties and plays an important role in drug design and development. Natural products are good source of lead compounds. Morphine, quinine, atropine etc are some of lead compounds isolated from natural sources and are in clinical use. But most of the lead compounds require structural modification to overcome their low activity and or unacceptable side effects. To develop an orally active compound, certain properties of the lead compound should be taken into consideration such as Lipinski's rule of five or Veber's parameters that help pharmaceutical scientists to select the best candidates for development and to reject those with a low probability of success.^{1,2} Computer based (in silico) molecular modeling (bioinformatics and cheminformatics) are quite useful for this purpose, because they are extremely fast and cost efficient and can be applied even when a compound is not physically available.³

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Boswellia species, commonly known as frankincense, have been used for centuries in traditional medicine as antiseptic, antiarthritic and anti-inflammatory remedies. *Boswellia serrata* (Salai guggal) is a moderate-to-large branching tree (growing to a height of 12 feet) found in India, Northern Africa, and the Middle East. The lipophilic fraction of the gum of Indian species, *B. serrata*, is used as an ayurvedic medicine for the topical treatment of joint diseases and various inflammatory (chronic) disorders.⁴ Dried extract of oilbanum is commercially available in the Indian as well as in international market and is used to treat various inflammatory disorders. Boswellic acids (BAs) are the major constituents (25–35%) of oleo gum resin derived from *Boswellia* species. Boswellic acid derivatives are pentacyclic triterpenoids belonging to ursane or oleanane groups.⁵ BAs comprise of mainly β -boswellic acid (BA, **1**) as the main triterpenic acid along with 11-keto- β -boswellic acid (KBA, **2**) and corresponding acetates ABA (**3**) and AKBA (**4**).⁶ BAs inhibit 5-lipoxygenase, COX enzymes, human leukocyte elastase and the nuclear factor- κ B pathway and prevent the synthesis of mediators of inflammation. BAs exhibit potent anti-inflammatory properties; without exerting the adverse effects known for steroids.⁷⁻⁹ Among the important derivatives of BAs, KBA and AKBA are known to be the most potent inhibitors of 5-lipoxygenase.¹⁰ Clinical studies have also shown boswellia to benefit patients with rheumatoid arthritis, inflammatory bowel diseases and cancer patients. Its concurrent use may help reduce cerebral edema in patients with brain tumors, helping reduce the need for steroids and their significant adverse side effects.^{11,12}

In continuation of our research to find a potential anti-inflammatory lead compound having high target selectivity, low toxicity and better bioavailability from natural sources, we have virtually screened the molecular properties for drug likeness and bioactivity score of four naturally occurring BAs (**1-4**), four semi synthetic derivatives of BAs having a fused pyrazole rings (**5-8**)⁶ and four AKBA derivatives (**9-12**)¹³ substituted at position 3 and 24 by using online Molinspiration software.

Fig 1. General structure of Boswellic acid and derivatives (1-4)

Number of the compound	Name of the compound	Substituent's
1	β - Boswellic acid (BA)	$R_1=R_2=H, R=H$
2	11- Keto β - Boswellic acid (ABA)	$R_1+R_2=O, R=H$
3	3- Acetyl β - Boswellic acid (ABA)	$R_1=R_2=H, R=COCH_3$
4	3- Acetyl -11- Keto β - Boswellic acid (AKBA)	$R_1+R_2=O, R= COCH_3$

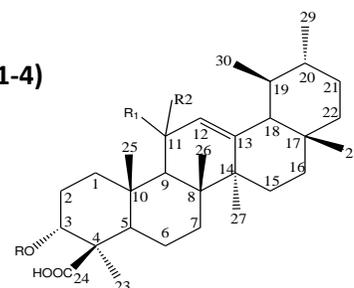


Fig 2. Pyrazole analogs of Boswellic acids derivatives (5-8)⁶

Number of the compound	Substituent's
5	$R_1=R_2=H, R=H$
6	$R_1+R_2=O, R=H$
7	$R_1=R_2=H, R=COOCH_3$
8	$R_1+R_2=O, R= COOCH_3$

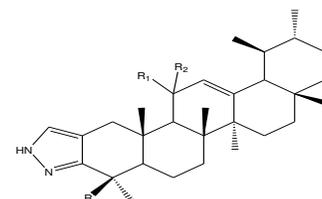
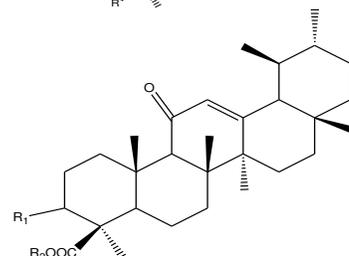


Fig 3. AKBA derivatives (9-12)¹³

Number of the compound	Substituent's
9	$R_1= OH, R_2= CH_3$
10	$R_1=OH, R_2=CH(CH_3)_2$
11	$R_1= (=O), R_2= CH_3$
12	$R_1=(=O), R_2=CH(CH_3)_2$



Materials and Method

Structures of all the selected BAs derivatives were drawn by using ACD labs Chemsketch v 12.0 and their SMILES notations were generated. Smiles notations of the selected compounds were fed in the online molinspiration software version 2011.06 (www.molinspiration.com) for calculation of molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The bioactivity score and drug likeness properties of the BAs derivatives were compared with the cortisol and Aceclofenac drugs.

Results and Discussion

The calculated values of various parameters of the isolated compounds for drug likeness are presented in the table 1. Drug likeness evaluates whether a particular molecule is similar to the known drug or not. It is a complex balance of various properties and structural features of a compound. Lipinski's rule is widely used to determine molecular properties that are important for drug's pharmacokinetic in vivo. According to Lipinski's rule of five¹, a candidate molecule is more likely to be orally active if: a) the molecular weight is under 500, b) the calculated octanol/water partition coefficient (log P) is less than 5, c) there are not more than 5 hydrogen bond donors (OH and NH groups), d) there are not more than 10 hydrogen bond acceptors (notably N and O). However, there are some exceptions to this rule and a compound is likely to be orally active as long as it did not break more than one of his rules because some of orally active drugs such as atorvastatin, cyclosporin do not obey the rule of five. Partition coefficient or Log P is an important parameter used in rational drug design to measure molecular hydrophobicity. Hydrophilic/lipophilic nature of drug molecule affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity. Log P values of BAs derivatives were found to be in the range of 5-688-7.899 and is a clear violation of Lipinski's rule of five. Compound **2** is expected to have the highest hydrophilicity because its log P value is just above 5, whereas compound number **5** will be the most lipophilic. This implies that these compounds will have poor permeability across cell membrane. Some structural modifications should be carried out to improve their oral absorption, bioavailability and permeability. Low molecular weight drug molecules (<500) are easily transported, diffuse and absorbed as compared to heavy molecules. Except compound **4**, **8**, **10** and **12**, molecular weight of all other compounds was found to be less than 500. Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) in the tested compounds were found to be within Lipinski's limit i.e. less than 10 and 5 respectively.

Total polar surface area (TPSA) is closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood brain barrier penetration etc. TPSA of BA derivatives was found in the range of 28.683-80.675 and is well below the 160 Å² limit. Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs.² Among all the screened compounds **3**, **4**, **10** and **12** were flexible (3 rotatable bonds) and compound **5**, **6** were rigid as they do not have any rotatable bond. The predicted bioactivity scores of screened compounds as well as their comparison with the standard drug for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear

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receptor ligand, protease inhibitor and enzyme inhibitory activity are summarized in Table 2. As a general rule, larger is the bioactivity score, higher is the probability that investigated compound will be active. Therefore, a molecule having bioactivity score more than 0.00 is most likely to possess considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is presumed to be inactive.¹⁴ The results of the present study demonstrated that the investigated compounds are biologically active molecules and will produce the physiological actions by interacting with GPCR ligands, nuclear receptor ligands, and inhibit protease and other enzymes. Though bioactivity score for GPCR ligand is found to be >0.00 for all tested compounds, but the highest score (0.24) was observed for **1** closely followed by **2** (0.23). Bioactivity score for ion channel modulator activity was in between 0.00 and -0.50 suggest their moderate interaction with this target. Similar results are obtained for kinase inhibition and only compound **1**, **3**, **5** and **7** showed score >-0.50, rest of the molecules were inactive towards this drug target. Bioactivity scores for nuclear receptor ligand, protease inhibitor and enzyme inhibition was found to be in the range of 0.51- 0.84, 0.08-0.33 and 0.43-0.66 respectively, suggest highly bioactive nature of molecules. The most promising compound was identified as **2** for which bioactivity score of 0.84, 0.36 and 0.66 was obtained for nuclear receptor ligand, protease inhibitor and enzyme inhibition respectively. Also it was observed that semisynthetic compounds (**9-12**) having substitution at 3 and 34 positions showed comparable activity with the naturally occurring BAs (**1-4**). It can be concluded that blocking position 3 by introducing heterocyclic ring decreases bioactivity, therefore, structural modifications should be carried out at either 3 and 24 or at both to obtain the molecules with better pharmacological activity.

Conclusion

It can be concluded that BAs derivatives are biologically important molecules and possess desirable molecular properties for drug likeness except log P values. Therefore, some structural modifications should be made in the skeleton of BAs to improve their hydrophilicity and bioavailability. Compound number **2**, 11-keto- β -boswellic acid emerged as a promising anti-inflammatory lead molecule as it showed higher bioactivity score in comparison to standard drugs, cortisol and aceclofenac and had only one violation of Lipinski's rule of five.

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Table 1: Drug likeness score for compounds (1-12)

Compd No.	miLog P	TPSA	nAtoms	nON	nOHNH	n violation	n rotb.	Volume	MW
1.	6.789	57.257	33	3	2	1	1	471.489	456.711
2.	5.688	74.598	34	4	2	1	1	473.671	470.694
3.	7.493	63.604	36	4	1	1	3	508.001	498.748
4.	6.392	80.675	37	5	1	2	3	510.182	512.371
5.	7.889	28.683	32	2	1	1	0	455.403	434.712
6.	6.788	45.754	33	3	1	1	0	457.584	448.695
7.	7.843	54.988	36	4	1	1	2	499.608	492.748
8.	6.742	72.059	37	5	1	2	2	501.789	506.731
9.	6.304	63.604	35	4	1	1	2	491.199	484.721
10.	7.043	63.604	37	4	1	2	3	524.588	512.775
11.	6.118	60.447	35	4	0	1	2	485.377	482.705
12.	6.858	60.447	37	4	0	2	3	518.726	510.729
Aceclofenac (std)	4.429	75.631	23	5	2	0	7	283.499	354.189
Cortisol	1.617	94.826	26	5	3	0	2	343.063	362.466

Table 2: Bioactivity score of the compounds according to Molinspiration Cheminformatics software

Compd No.	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1.	0.24	0.02	-0.44	0.79	0.33	0.62
2.	0.23	-0.05	-0.63	0.84	0.36	0.66
3.	0.16	-0.02	-0.49	0.69	0.28	0.55
4.	0.15	-0.10	-0.66	0.74	0.31	0.59
5.	0.21	-0.14	-0.39	0.51	0.08	0.46
6.	0.18	-0.23	-0.61	0.53	0.11	0.46
7.	0.16	-0.24	-0.44	0.51	0.05	0.30
8.	0.13	-0.34	-0.62	0.52	0.08	0.30
9.	0.16	-0.06	-0.59	0.74	0.31	0.57
10.	0.14	-0.12	-0.58	0.72	0.27	0.54
11.	0.08	-0.15	-0.70	0.66	0.10	0.45
12.	0.06	-0.21	-0.69	0.65	0.09	0.43
Std I	0.14	0.06	0.13	0.03	-0.01	0.15
Cortisol	0.0	-0.29	-0.85	1.17	0.09	0.63