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New derivatives of 11-keto-β-boswellic acid (KBA) induce apoptosis in breast and prostate cancers cells

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ABSTRACT

A series of new 11-keto-β-boswellic acid were partially-synthesized by modifying the hydroxyl and carboxylic acid functional groups of ring A. The structures of the new analogs were confirmed by detailed spectral data analysis. Compounds **4**, **5** and **9** exhibited potent anti-cancer results against two human tumor cancer cell lines having IC_{50} value of MCF-7 (breast) and LNCaP (prostate): 123.6, 9.6 and 88.94 μM and 9.6, 44.12 and 12.03 μM, respectively. Additionally, a maximum nuclear fragmentation was observed for **4** (78.44%) in AKBA treated cells after 24 hr followed by **5** and **9** with (74.25 and 66.9% respectively). This study suggests that the presence of hydrazone functionality (**4** and **9**) has effectively improved the potency of AKBA. Interestingly, compound **5** with a lost carboxylic acid group of ring A showed comparable potent activity. Highly selective AKBA requires further modification to improve its bioavailability and solubility inside the cancer cells.

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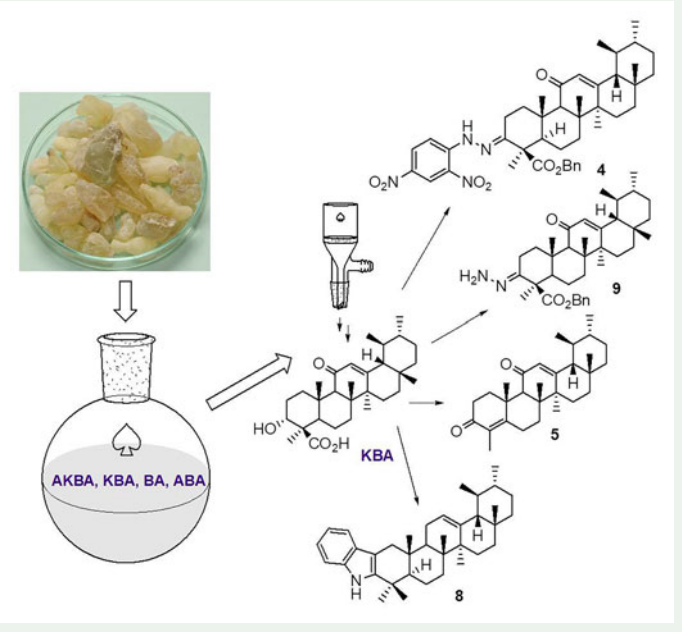


1. Introduction

Number of annual deaths due to cancer is dramatically increasing worldwide despite the advances in the treatment strategies. Natural compounds or their derivatives are major sources of anticancer drugs and it has been reported that over 150 natural products-derived drugs are amiable in market between 1981 and 2014 (Baskar et al. 2012). Evidences from tissue culture, animal, and clinical studies suggest that more than 20,000 natural triterpenoids have the potential ability to limit the development and severity of certain cancers (Newman and Cragg 2016; Laszczyk 2009) Pentacyclic triterpenes such as ursane and oleanane-type play an important role in cancer treatment with different modes of action (Sun et al. 2006). These triterpenes exhibit significant antitumor activity and the chemical modification of these triterpenes results in enhancing anti-tumor activities (Csuk et al. 2015; Kumar et al. 2016)

Various triterpenes have been reported from the resins of *Boswellia* species (frankincense). Boswellic acids are either oleanane or ursane-type having carboxylic acid at C-4. They demonstrated antimicrobial, antidiabetic, antiviral, antipruritic and anti-inflammatory activity (Kumar et al. 2016). The family consists of β-boswellic acid (β-BA), a pentacyclic triterpenic acid, and its natural derivatives: 3-acetyl-β-BA (β-ABA), 11-keto-β-BA, and 3-acetyl-11-keto-β-BA (Kumar et al. 2016; Raja et al. 2011; Safayhi et al. 1992; Hamidpour et al. 2013). AKBA suppresses NF-κB signaling and to noncompetitively inhibit 5-lipoxygenase, topoisomerase and leukocyte elastase (Csuk et al. 2015). AKBA has also shown to exert apoptotic actions on various cancer cell lines through induction of caspase-3 and caspase-8 as well as with poly(ADP)ribose polymerase (PARP) cleavage (Lu et al. 2008). The anticancer activity of AKBA remains in micro

molar with IC_{50} dose 10–100 μM (Yuan et al. 2008; Park et al. 2002; Siddiqui 2011; Liu et al. 2013; Jing et al. 1999).

The current study aims to increase the potency of AKBA via modification of ring A and synthesis of heterocyclic analogs. This project begins with structure–activity relationship (SAR) studies in which various functional groups of the small molecule of interest are added or removed to determine the derivative that increases potency and selectivity of AKBA. Triterpenoids with 30 carbon atoms derived from cyclization of squalene, oleanane and ursane type of triterpenoids that exhibit antitumor activity by the substitution of cinnamoyl moiety in their structures (Sun et al. 2006). Saponin is well known triterpene, amide substitution at C-28 of saponin results in highly cytotoxic derivatives for specific tumor cell lines, and also leads to an increase in the antitumor selectivity of β-hederin (Thakur et al. 2011). Further incorporation of carbonyl group at C-16, additional sugar unit viz., L-rhamnose at C-3 and acetyl group at C-6 of the D-glucose in various saponins lead to a significant increase of the cytotoxic activity against various cancer cells (Mu et al. 2013). Synthetic addition of 13,28-epoxy, 16 α-hydroxy, and C-30 methyl moieties in the saponins selectively inhibited the growth of liver cancer (Bel-7402 and HepG-2) cells without affecting the survival of normal liver (HL-7702) cells (Li et al. 2012). Hydrazone represents an important class of compounds with broad spectrum of pharmacological activities with a highly reactive group (CO-NH-N = CH) (Verma et al. 2014).

2. Results and discussion

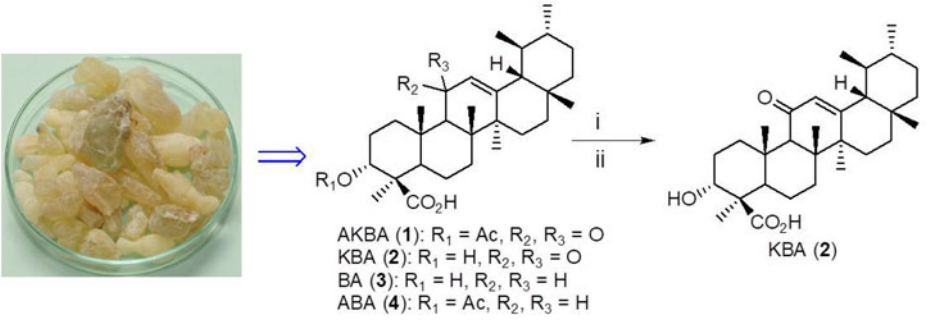
2.1. Chemistry

2.1.1. The preparation of 11-keto-β-boswellic acid (KBA)

Boswellic acids were extracted from Omani frankincense tree (*B. sacra*) using the protocol described earlier (Csuk et al. 2015). The concentration of BA, KBA, ABA and AKBA vary significantly depending on the *Boswellia* species as well as on the environmental factors within the same species (Al-Harrasi et al. 2018). In order to enrich the content of KBA, we followed Jauch and Bergmann focused approach (Jauch and Bergmann 2003) and converted AKBA to KBA and ABA into BA via deacetylation. This is followed by conversion of BA to KBA employing allylic photo-oxidation which introduced carbonyl group at C-11 (Jauch and Bergmann 2003) (Scheme 1).

2.1.2. The preparation of new derivatives of KBA

In order to synthesize different derivatives of KBA, the carboxyl group in KBA was protected using benzyl bromide in the presence potassium carbonate which afforded ketone in **1a** in 91% yield. This was followed by oxidation of the hydroxyl group at C-3 using Jones reagent which furnished 3-keto derivative **2** in 86% yield. Similarly, the natural 3-epi-α-amyrin **6** was oxidized to α-amyrenone **7** using Jones reagent. This was followed by treating **7** with phenylhydrazine to give the indole derivatives **8** in 67% yield. Interestingly when compound **2** was treated with 2,4-dinitrophenylhydrazine under identical conditions described for synthesis of **8**, the expected indole derivative was not formed, instead hydrazone **4** was isolated in 73% yield. This is likely due



Scheme 1. Jauch and Bergmann (2003) 'Focusing' approach to large-scale synthesis of KBA (**2**). Reagents and conditions: (i) 0.5 N KOH in *i*PrOH, reflux, 15 hr; (ii) NBS/$CaCO_3$/H_2O, dioxane, hν, rt, 10 hr.

to the presence of two electron withdrawing nitro groups at positions 2 and 4. In a similar manner, hydrazone **9** was obtained from the reaction of **2** with hydrazine.

Brominated derivative **3** was obtained in 81% yield by reaction of diketone **2** with $CuBr_2$ which upon treatment with Li_2CO_3 and LiCl, decarboxylated derivative **5** was isolated in relatively low yield (Scheme 2).

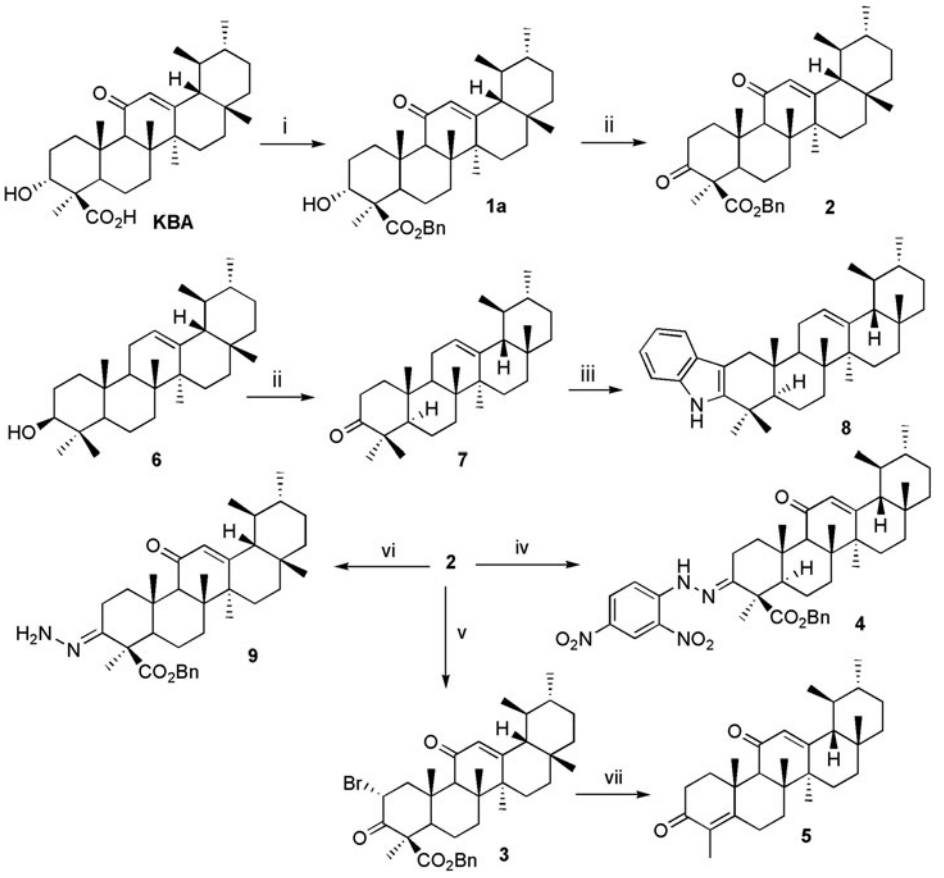
2.2. Biological assays

2.2.1. Cytotoxicity of natural compounds of boswellic acids

Cytotoxic effects of boswellic acid derivatives were studied against two human cancer cell lines: human breast cancer (MCF-7) and human prostate cancer (LNCaP) using doxorubicin as positive control. The effects were also studied on normal human nasal epithelial cell line (RPMI2650). Analysis of the two natural triterpenes derivatives of boswellic acid, KBA and AKBA, showed that AKBA showed more potent inhibition of cellular survival with IC_{50} dose of 75.4 μM and 21.0 μM on MCF-7 and LNCaP cell lines, respectively, Figure S1A and B. Breast adenocarcinoma MCF-7 cell lines were more pre-apoptotic-sensitive with AKBA with pre-apoptosis EC_{50} dose of 2.4 μM compared to LNCaP cell lines with EC dose of 21 μM, Figure S1A and B. The IC_{50} of KBA was 3.7 fold less effective on MCF-7 compared to AKBA. Cytotoxic effects of both AKBA and KBA were induced at higher dose when normal human cell lines were used, Figure S1C. This shows less cytotoxic effects on normal cell line compared to breast and prostate cancer cell lines. Figure S1D shows an example of flow cytometry scatter plot live, dead and preapoptotic cells.

2.2.2. Derivatives with no enhanced potency compared to AKBA

Some of the AKBA derivatives showed lower activity compared to the natural AKBA, Table 1, and Figure S3. Loss of acetyl group as in **1** and **2** (line b and c in Figure S2) showed reduced cytotoxicity with IC_{50} dose of 107 μM and 181.3 μM on MCF-7 cell lines respectively. On the other hand, MCF-7 cell lines underwent pre-apoptosis with these two derivatives at EC_{50} value of 5.2 μM and 6.3 μM, respectively. Prostate cancer cell lines (LNCaP) exhibited more sensitivity against these two derivatives with IC_{50} dose of 25.62 μM and 98.6 μM respectively. Loss of carboxylic group in KBA as in **6**



Scheme 2. Reagents and conditions: (i) BnBr, K_2CO_3, DMF, rt, 12 hr, **1** (91%), **7** (84%); (ii) Jones reagent, rt, 2 hr, **2** (86%) (iii) Phenylhydrazine, AcOH, reflux, 6h, **8** (67%) (iv) 1-(2,4-dinitrophenyl) hydrazine, AcOH, reflux, 6 hr, **4** (73%); (v) $CuBr_2$, CH_2Cl_2-EtOAc, reflux, 3 hr, **3** (81%); (vi) Hydrazine, AcOH, reflux, 48 hr, **9** (64%) (vii) Li_2CO_3, LiCl, DMF, reflux, 8 hr, **5** (48%).

decreased the potency with IC_{50} dose of 114.9 μM and 133.7 μM on MCF-7 and LNCaP cell lines, respectively, Figure S2 (line d). Indole derivatives are important structures of antitumor drug design; however, this moiety in **8** did not show enhanced anti-cancer activity with IC_{50} of 294.5 μM on MCF-7 cell line (Figure S3 line e). Likewise, addition of bromo-group in **3** did not improve the cytotoxic activity on breast cancer cells where IC_{50} dose was 123.6 μM, Figure S2 line f.

2.2.3. Derivatives with enhanced potency compared to AKBA

Survival and pre-apoptosis data revealed that structure-activity relationships (SAR) play a crucial role in the cytotoxic activity of AKBA analogs. As illustrated in Figure S3, hydrazone **4** demonstrated increased anticancer activity in LNCaP with IC_{50} of 9.6 μM when compared to AKBA (21 μM) (Figure S3B). MCF-7 cell lines were less sensitive to hydrazone analog (**4**) with IC_{50} of 123.6 μM (Figure S3A) compared to AKBA. Hydrazide-hydrazone derivatives containing a highly reactive group (CO-NH-N = CH) are reported to be good candidates for development of a new drugs (El-Faham et al.

Table 1. IC_{50} and EC_{50} of less-potent AKBA derivatives.

	MCF-7		LNCaP		RPMI2650	
Compounds	Survival IC_{50} (μM)	Pre-apoptosis EC_{50} (μM)	Survival IC_{50} (μM)	Pre-apoptosis EC_{50} (μM)	Survival IC_{50} (μM)	Pre-apoptosis EC_{50} (μM)
AKBA	75.4 (50–112)	2.4 (0.07–7.8)	21 (12–36)	21 (12–36)	1014 (260–3942)	1006 (161–886)
1	107.7 (61–187)	5.2 (0.6–46)	25.6 (13–50)	25.6 (12–50)	261.8 (113–602)	263.4 (114–607)
2	181.3 (110–296)	6.3 (1.4–27)	98.6 (47–205)	98.4 (47–205)	104.6 (38–285)	106.4 (39–289)
6	114.9 (60–222)	435.2 (1×10^{-4}–1.2×10^{11})	133.7 (51–353)	133.7 (50–353)	523.1 (189–1445)	530.8 (194–1450)
3	123.6 (56–275)	72 (26–196)	21.2 (11–42))	21.1 (11–42)	84.18 (27–261)	90.8 (30–271)
8	294.5 (170–508)	51.3 (26–100)	19.6 (7–54)	19.6 (7–53)	150.6 (75–302)	172.6 (87–340)
Doxorubicin	0.0098 (0.007–0.012)	—	0.188 (0.09–0.33)	—	0.0164 (0.008–0.03)	—

MCF-7 = breast cancer; LNCaP = prostate cancer; RPMI2650 = normal cell lines. Brackets show the 95% confidence intervals.

2015). In addition, their anti-cancer activity has been reported (Terzioglu and Gürsoy 2003; Boga et al. 2009; el-Sabbagh and Rady 2009) and are considered one of the most efficacious low-molecular drugs for the treatment of breast cancer (Biersack and Schobert 2012; Sidhu et al. 2015). Compound **5** demonstrated better anticancer effects towards MCF-7 and LNCaP cell lines with IC_{50} value of 44 μM and 9.6 μM, respectively. In addition, compound **5** started to induce pre-apoptosis at extremely low dose with EC_{50} of 0.09 μM on MCF-7 cell lines. More activity was observed on LNCaP cell line than MCF-7 with IC_{50} dose of 12.03 μM and 88.94 μM, respectively.

One of the greatest challenges in cancer drug discovery is the selective killing of cancer cells. Natural products are gaining a great attention to act as promising cancer-specific cytotoxicity. It is worth noting that AKBA reflected a remarkable selectivity where IC_{50} and EC_{50} values on normal cell lines (RPMI2650) were 1014 μM and 1006 μM, respectively (Figure S3C). On the other hand, the potent compounds (**4, 5** and **9**) showed cytotoxicity on normal cells as illustrated in Figure S3C. This finding suggests that AKBA is a promising anticancer drug that may provide an alternative to chemo and radiotherapy.

2.2.4. Chromatin condensation assay using Hoechst 33342 stain

To gain further insight into the cytotoxic effect of the compounds, we investigated the nuclear changes and condensation using Hoechst 33342 stain on MCF-7 cells. Apoptosis is morphologically characterized by cell shrinkage, chromatin condensation and nuclear fragmentation. The results of this assay revealed that potent compounds inducing apoptosis in MCF-7 cells and the effect was found to be increased with increasing doses of the compounds (Table 2). Fragmentation of nuclei, a characteristic feature of apoptosis, was observed in compounds-treated cells after staining with Hoechst. Maximum nuclear fragmentation occurred in AKBA treated cells for 24 hr followed by compound **5** and **9** with percentage 78.25, 74.25 and 66.9% respectively.

2.2.5. Effect of potent compounds on cellular signaling

Different signaling apoptotic pathways were investigated for the effects of AKBA and its potent derivatives. AKBA treatment showed reduction in levels of caspase-3 and PARP, Figure S4. Western blot data indicate inhibition of PARP1 in cells treated by potent derivatives (**4, 5** and **9**), thereby initiating the apoptosis pathway in both cell lines. Protein levels of pro and active PARP1 were strongly reduced by these derivatives making them future candidate of PARP inhibition. Several PARP inhibitors are in advanced stages of clinical development for several tumor types. In breast and ovarian cancer clinical trials, PARP inhibitors showed increased activity in platinum-sensitive

Table 2. Nuclear fragmentation percentage of the potent AKBA derivatives.

	Nuclear Fragmentation (%)			
Compounds	0 hr	9 hr	12 hr	24 hr
AKBA	30.5 ± 3.06	54.25 ± 1.53	63.0 ± 2.89	78.25 ± 2.65
4	32.93 ± 8.89	54.8 ± 4.04	59.99 ± 1.53	70.49 ± 2.08
5	32.28 ± 7.37	40.75 ± 3.06	56.5 ± 8.14	74.25 ± 4.16
9	28.5 ± 2.65	53.26 ± 5.03	63.4 ± 6.11	66.9 ± 9.88

Experiments were performed in triplicate in three separate experiments and results are expressed as mean ± standard deviation (mean ± SD).

tumors, making PARP an attractive candidate in cancer therapy (Lu et al. 2008). We only detected expression of pro-caspase-3 without the cleaved active form. Absence of active caspase-3 levels may suggest non-classical AKBA-induced apoptosis. Such apoptotis is present in normal oral epithelium, keratinocytes and squamous cell carcinoma (Gandarillas et al. 1999; Hague et al. 2004; Lippens et al. 2000). All these data suggests that the potent derivatives of AKBA may act as future candidate for anti-cancer drug development. Although multiple signaling pathways are affected, with profound effect on PARP and STAT3 signaling, it yet unclear about the cellular target of AKBA. Future proteomic profiling and drug-protein binding assays are warranted.

3. Conclusion

Natural products are gaining a lot of interest due to their affectivity and selectivity. In this study, eight AKBA derivatives were synthesized as anticancer drugs. The anti-proliferative effects of these compounds were determined in breast and prostate cancer cell lines (MCF-7 and LNCaP), and the structure-activity relationships (SAR) were analyzed. Synthetic efforts were mainly directed toward the modification in ring A and C-24 carboxyl group with different substituents to evaluate the effects of functional groups on anti-proliferation activities. Moreover, among all tested compounds, three compounds (**4, 5** and **9**) exhibited the best potency. Despite of potency of the derivatives, the natural AKBA showed greater selectivity on cancer cells over the normal cell line (RPMI2560). This feature of AKBA overcomes the adverse effect of chemo and radiotherapy on normal cells. For instance, Doxorubicin exhibits very low IC_{50} value of 0.164 μM compared to 1014 μM of AKBA on normal nasal cell line (RPMI2560) (Drug: Doxorubicin - Cancerrxgene - Genomics of Drug Sensitivity in Cancer). However, AKBA displays drawback in its poor oral bioavailability due to its high lipid solubility, rapid phase-1 metabolism and poor intestinal permeability (Miller et al. 2016; Bhardwaj et al. 2016). Future research is required to improve AKBA bioavailability and solubility through different drug delivery system nanoparticles (Ding et al. 2016), nanomicelles (Goel et al. 2010), liquisolid systems (Mostafa, Nagwa, Abd El-Alim, et al. 2015), new water soluble glycosides (Manjunath et al. 2018), and transdermal microemulsions (Mostafa, Nagwa, Mona, et al. 2015).

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Disclosure statement

The authors declare no conflict of interest with respect to this study.

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