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Anti-proliferative Evaluation of Monoterpene Derivatives against Leukemia

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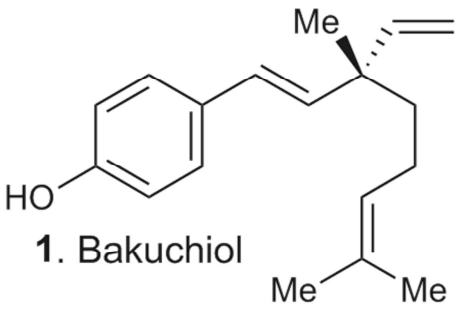
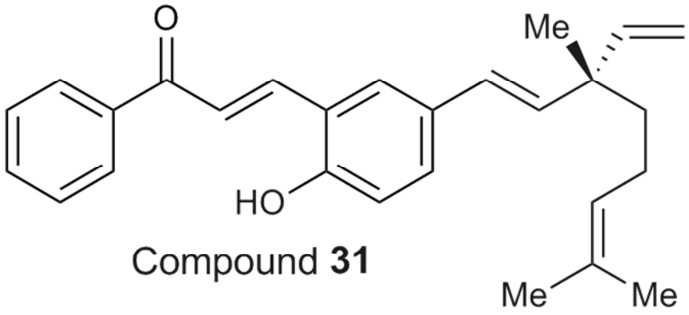


1. Bakuchiol

SEM EC_{50}= 15.28 μM

HepG2 EC_{50}>52.08 μM



Compound **31**

SEM EC_{50}= 8 μM

HepG2 EC_{50}>52.08 μM

Anti-proliferative Evaluation of Monoterpene Derivatives against Leukemia

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Abstract

The cure rate of pediatric acute lymphoblastic leukemia (ALL) has significantly improved in the past thirty years, however not all patient cohorts respond well to current chemotherapy regimens. Among the high risk patient cohort is infants with MLL-rearranged (MLL-r) B-ALL, which remains dismal with an overall survival rate <35%. Our program is interested in identifying new molecular scaffolds to better understand the underlying mechanisms and ultimately provide new targeted treatments. Based on a phenotypic screen, phenolic natural products were identified as promising scaffolds for further chemical evaluation. Herein we disclose the effects of a potent anti-proliferative compound **31** against human ALL leukemia cellular models.

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Introduction

Natural products (NPs) are an integral component of drug discovery programs and have been successfully implemented in the oncology field. Approximately 60% of clinically approved anticancer drugs are based on secondary metabolites found in nature [1]. Terrestrial NPs are rich and a relatively untapped source of molecular scaffolds for the development of tool compounds and/or therapeutic agents [2]. Our research is focused on identifying new lead compounds from NPs against leukemia. Using NP fractions, phenotypic screens were conducted on stable B and T human leukemic cell lines. In a preliminary screen, we identified bakuchiol and curcumin as active compounds against B cells in the 30-40 μM range. This account describes the synthesis and evaluation of bakuchiol derivatives against acute lymphoblastic leukemia (ALL).

(S)-Bakuchiol (BA, Fig. 1) is a prenylated phenolic monoterpene isolated from *Psoralea corylifolia Leguminoesae*, widely use in Chinese and Indian traditional medicine [3]. Monoterpenes are naturally occurring hydrocarbons composed of the condensation of two isoprenes. They are widely distributed in the plant kingdom and are mostly recognized as plant essential oils. BA has been reported to exert anticancer, anti-bacterial, and anti-inflammatory biological activity [3-7]. Cytotoxicity properties on hematological cancer cell lines have been reported for curcumin [8], but to our knowledge, not for BA. We hypothesized that hybrid molecular scaffolds of BA and curcumin would provide compounds with improve biological potency and selectivity towards ALL cellular models. The optically active BA features a quaternary carbon center, bearing a vinyl group, and an isoprene unit that can be chemoselectively differentiated. Representative members (**2-7**, Fig.1) of this natural product family share a phenolic core and different levels of complexity/biological activity [9]. Our central objective was to develop NP **1** derivatives at C3-C4, C12-C13 and C18 to evaluate their biological properties against ALL cellular models.

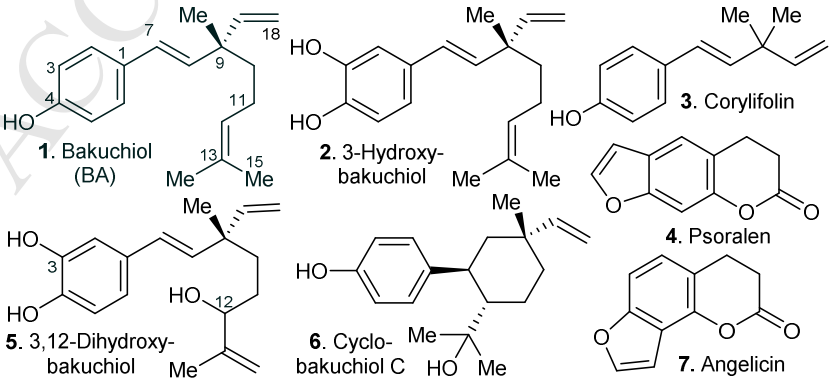

Figure 1. Constituents of *Psoralea corylifolia* and related natural products.

ALL is the most common cancer among children and the most frequent cause of death for those under 20 years of age in industrialized nations [10]. Although, five-year cure rates are high for most ALL cases, two of its subgroups remain challenging and would benefit from the discovery of new therapeutic agents, infant ALL and glucocorticoid resistant ALL [10]. The human AF4 (ALL-1 fused gene on chromosome 4) gene (4q11) is recurrently involved in reciprocal translocations to the mixed lineage leukemia (MLL) gene (11q23), and correlates with high-risk ALL in infants and early childhood [11]. Outcome of infants with MLL-rearranged (MLL-r) B-ALL with a pro-B/mixed phenotype remains dismal, displaying a particularly poor prognosis. To identified potential lead compounds, a high throughput screen including the B cells (Nalm06, Nalm16, 697, Reh, SEM) and the T cells (Jurkat, CEM, Molt-3, Loucy) was conducted. The disclosed study focuses on the SEM (a model for MLL-r B-ALL) and the pre-B cell Nalm06 (a standard model for B cell ALL).

Results and Discussion

The synthetic strategy focused on chemical modification of BA, which was isolated from seeds of *Psoralea corylifolia* as pure oil in 3% yield by mass, as the starting material. Derivatization at three regions of the molecule (Fig. 2) was feasible as orthogonal reactions were available for structure activity relationship studies (SAR). The phenolic C4-center can be *o*-alkylated or displaced by an aryl group or heteroatom. The C3, ortho-position of the phenol group can be activated, allowing for the introduction of alkyl groups. The appended olefin at C9 can be exploited through Palladium-mediated reactions and the isoprene unit can be readily oxidized to be extended through homologation reactions [12]. With sufficient compound **1** at hand, several chemical transformations at C3-C4, C12-C13 and C18 were amenable for biological evaluation (Fig. 2).

Our synthetic studies began with a global evaluation of the natural product **1** to better understand potential sites of relevant SAR. Etherification of the phenol provided compounds **10**-**13** under nucleophilic conditions in almost quantitative yields, while overall double bond hydrogenation of **1** yielded compound **14**. Chemoselective epoxidation using mCPBA and osmium mediated dihydroxylation of **1** afforded compound **15** and **16** respectively [13]. Oxidative cleavage of diol **16** resulted in aldehyde **17**, which was reduced to afford the corresponding alcohol **18**. Further derivatization of aldehyde **17** through treatment with stabilized or *in situ* prepared ylide reagents [14] provided the corresponding compounds **19**-**22**, and the corresponding hydrazine **23**. Allylic oxidation of C14 (or C15) with SeO_2 in AcOH [15] resulted in aldehyde product **24**, and the corresponding reduced

allylic alcohol **25**. Homologation reactions of aldehyde **24** yielded compounds **26-28**. The isolated yields of these compounds were in modest to good (67-98%, see SI for detail information).

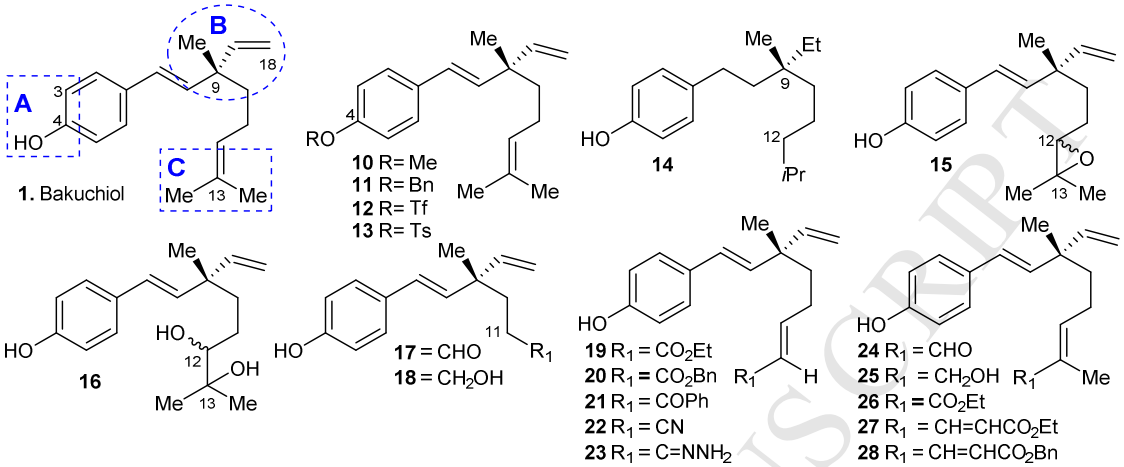

Figure 2. BA derivatives at C4 and C11-C12.

Next synthetic modifications of C3 and C18 were carried out to introduce aliphatic and aromatic functional groups at these centers for a thorough evaluation of the chemical space and electronic properties of this scaffold [16]. First regioselective ortho-formylation of the substituted phenol using the $MgCl_2$–Et_3N base system and paraformaldehyde under refluxing conditions [17] afforded the ortho-aldehyde **30**, which was reduced with $NaBH_4$ to generate alcohol **29** in excellent yields. Compound **30** was treated with stabilized ylide reagents [12] in benzene under refluxing conditions to produce a library of compounds, including electron-withdrawing groups **31-41**, and electron-donating groups (**42**) at C3 (75-80% yield, Fig. 3).

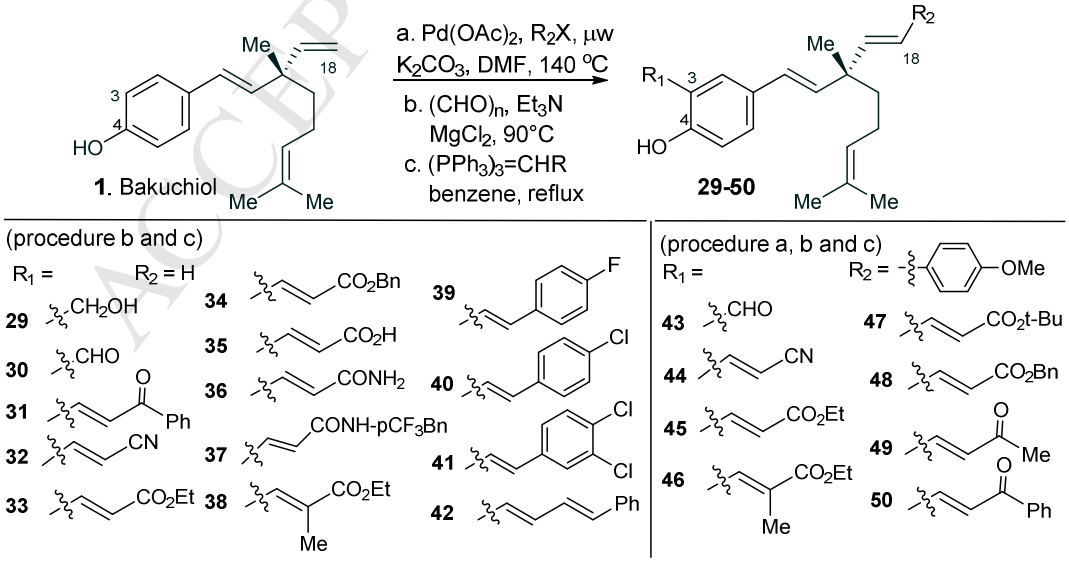

Figure 3. BA analogs evaluating C3 and C18.

Furthermore, compound **1** was evaluated under the Heck-Matsuda reaction (Fig. 3, and 4). Successful Heck-Matsuda arylation reactions of non-activated olefins applying microwave irradiation and heat can generate compounds bearing electron-donating or electron-withdrawing groups in good to excellent yields with reduced reaction time [18]. One of the disadvantages of the original reaction without microwave irradiation requires long reaction times that result in several side products, reducing the reaction efficiency of metal catalyzed coupling reaction.

Compound **1** was treated with 1-iodo-4-methoxybenzene, $Pd(OAc)_2$ and base (K_2CO_3, which offers excellent functional group tolerance and high efficiency) to introduce the *p*-OMe Aryl group at C18 to evaluate the effects of substitution at this center. The resulting intermediate was *o*-formylated to generate compound **43**, which was reacted with stabilized ylide to produce compounds (**44**-**50** in 70-80% yield, Fig. 3).

Next, we evaluated other functional groups on C18 by the introduction of other substituted aryl groups through the Heck-Matsuda reaction conditions previously described. BA was treated with either Pd (0) or Pd (II) along with the halogenated aryl, K_2CO_3 and base in DMF. The reaction was carried out under microwave conditions to afford compound **51**-**57** (Fig. 4) in modest to good yields (70-80%).

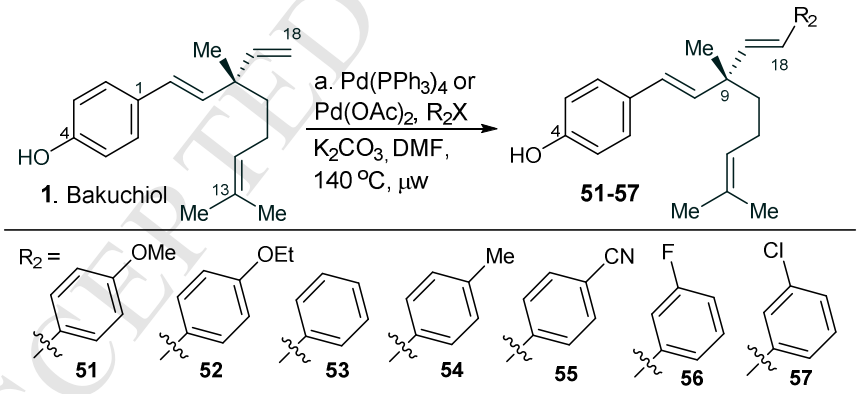

Figure 4. BA analogs evaluating C18.

Finally, we investigated coupling reactions at the C4 of BA to introduce either amines or alkyl groups. Despite the abundant number of reaction conditions to mediate C–N coupling reactions, only a relatively limited number has practical applications in terms of catalyst system, ligand availability and scope of substrate. The Buchwald-Hartwig reaction is one of the most reliable reactions [19]. The palladium catalyzed amination was conducted with the corresponding triflated phenol of BA, which subsequently treated with aryl amine, $Pd(OAc)_2$, and Cs_2CO_3 (provided the best tolerance and highest

reaction rate over other bases) in DMF. The catalytic presence of the ligand (2, 2'-bis(diphenylphosphino)-1,1'-binaphthyl, (±)-binap) facilitated the reaction in good yield to provide compounds **58**-**76** (75-80%, Fig. 5). Oxidative addition of benzyl, and aryl halides was performed under Suzuki-Miyaura reaction conditions [19]. The cross-coupling reaction of the aryl organoboronic acid compounds with triflated phenol of BA proceeds smoothly in DMF to effectively afford compounds **77**-**83** (60-80% yield, Fig. 5).

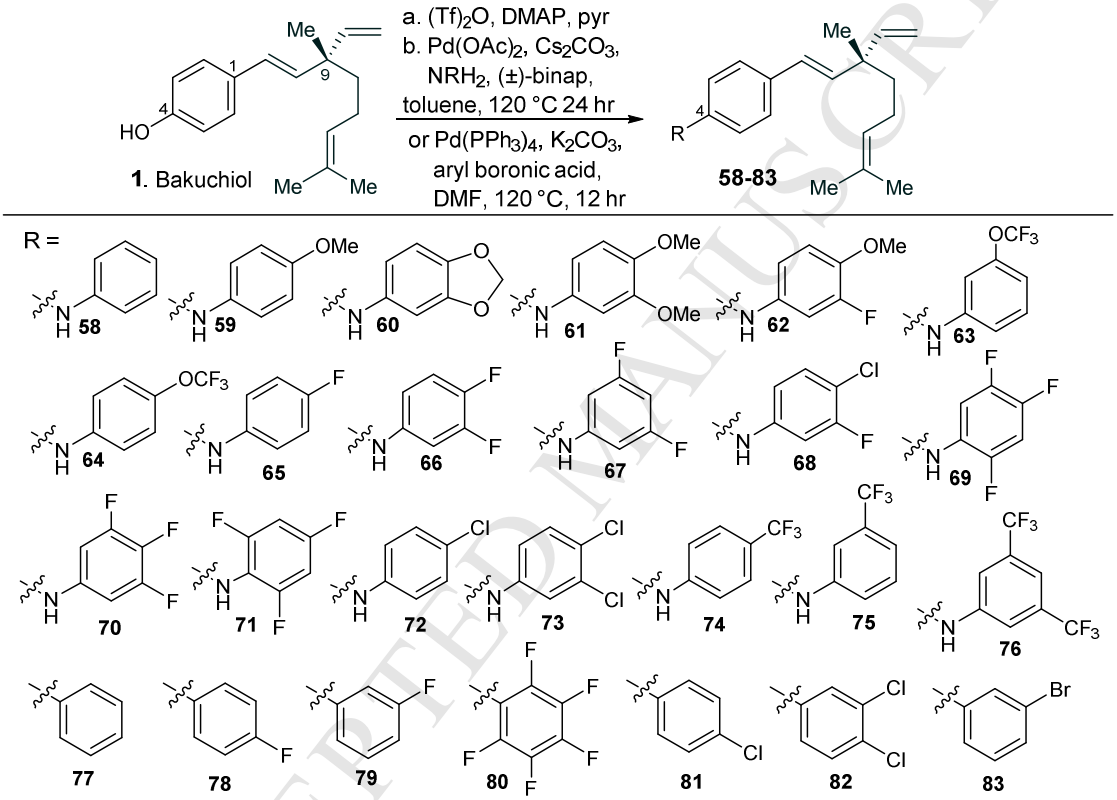

Figure 5. BA analogs evaluating C4.

A representative of the tested compounds is shown in table 1. The SAR indicate that i) the substitution pattern in the phenyl part of BA showed sensitivity towards modification with promising results at C3 (**30**-**36**) ii) modification at the isopropylidene group showed some activity (**14**-**16** against Nalm06, while no significant difference was observed between SEM and BJ cells), iii) modification at terminal olefin resulted in greater potency when an electrophile was present against Nalm06 or SEM (**24**, **43**, table 1). Some of the compounds were globally cytotoxic such as compound **44** with no therapeutic window. Furthermore, the study showed that addition of a hydroxyphenyl or mono methoxyphenyl moiety at C4 plays an important role in the biological activity. The most potent

compound that was identified was compound **31**, with an EC_{50} of 4.5 µM against Nalm06 and 8.0 µM against SEM while it displayed some toxicity in BJ (>20 µM), but no toxicity was observed in the HEPG2 cells at the tested concentrations (<90 µM). Interesting, compound **50** (which differs from compound **31** by the *p*-OMePh at C18) showed some activity against SEM (30 µM), no effect on NALM06, and EC_{50} higher than 36 µM in BJ and no toxicity against HEPG2. Despite the fact that compound **31** carries a Michael acceptor, it shows promise and further derivatization will provide a lead compound suitable for *in vivo* work. In the meantime, this compound will serve as a tool compound to identify the biological target and understand the involved biochemical pathways.

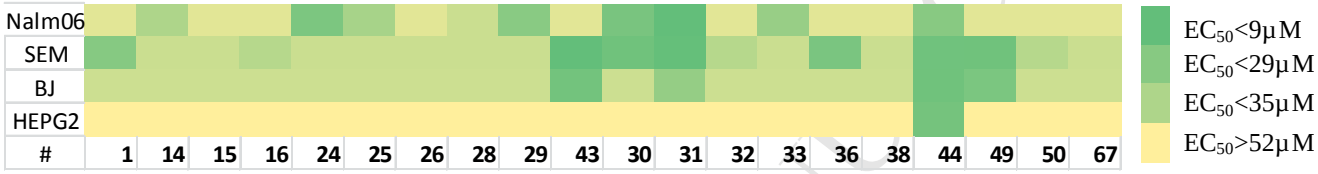

Table **1.** Representative heat map of selected compounds.

From a mechanistic perspective, here we focused our attention on the effects of compound **31** and used compound **51** as a negative control on (a) cell growth and cell cycle progression. Flow cytometric analysis was performed for cell cycle progression and apoptosis studies. Western immunoblotting was utilized to investigate if JNK was involved and end point markers of apoptosis. The MAPK, c-Jun NH_2-terminal protein kinase (JNK) has been proposed to play an important role in the regulation of apoptosis. Fluorochrome-labeled Annexin V and DNA content with PI [21] were studied treatment with compound **31** for a 24 hr period in SEM and Nalm06 to confirm apoptosis, or programmed cell death (for complete data set see SI). Representative images of 3 independent experiments are shown for negative control (DMSO), positive control (1 µM staurosporine) and 8.0 µM compound **31** for 24 hr treatment (Fig. 6).

Data presented on SEM cells (A. DMSO, B. 1 µM of Staurosporine, C. 8.0 µM **31**) and Nalm06 (D. DMSO, E. 1 µM of Staurosporine, F. 8.0 µM **31**) shows that after 24 hr treatment under this conditions, the cultured cells were captured in the late apoptotic state (Fig. 6). Both panels C and F depict over 80% of the cells were in late apoptotic state (Q2), with the remaining cells entering early apoptosis with only less than 3% cells remaining viable. Next, DNA content of the cells was measured to monitor cell proliferation and cell cycle. Proliferating cells progress through various phases of the cell cycle (G0, G1, S, G2, and M phase) and serum starvation is a widely used method to synchronize cells in a culture into the G0/G1 phase. This experiment was design to capture the exact changes in the cells upon treatment

with compound **31** for 24 hours under culture conditions. Graphical quantitation of the respective cell cycle phases for compound **31** versus DMSO control (Fig. 6, G) showed that 36.25% of cells were in the G0/G1 phase, 55.75% in the S phase, and 8.00% in the G2/M phase. While the DMSO control showed 45.75% increase in the G0/G1 phase, 46.62% in the S phase, and 7.63% in the G2/M phase. These results indicate that, as expected, the SEM cells used in this study were responsive to compound **31**, appeared to have arrested in S phase (ModFit LT™ plots are included in the SI for detailed account).

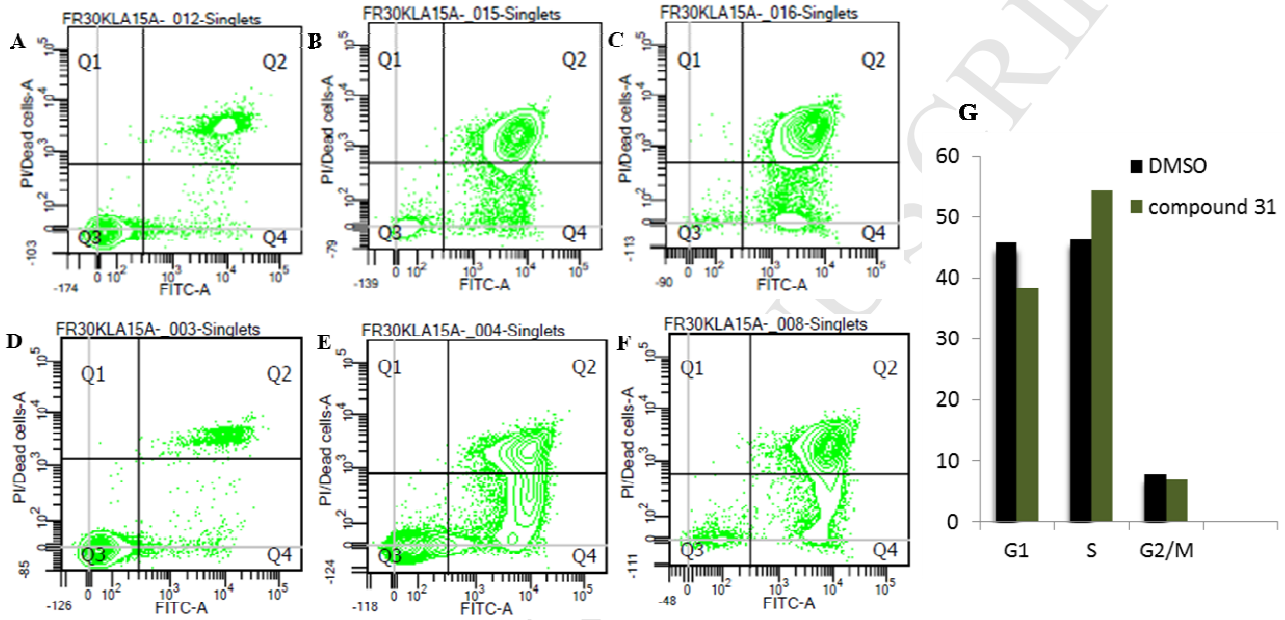

Figure 6. Representative Annexin V and cell cycle for SEM (A negative control, B. positive control, C. 31) and Nalm06 (D. negative, E. positive, F. **31**) and cell cycle for SEM.

The activation of caspase proteases is a critical event in the induction of apoptosis [22] so this process was investigated for compound **31** in a time-dependent by immunoblot analysis as shown in Figure 7. Compound **31** induced caspase-3, caspase-7-dependent apoptosis *in vitro* as well as PARP cleavage in both Nalm06 and SEM cell lines. The cells were treated with compound **31** for 3, 6, 12 and 24 hr at concentrations of 8.0 µM for SEM and 4.5 µM for Nalm06. As negative controls, DMSO (vehicle) and compound **51** were utilized at 20 µM. Significant caspase-3- activity was induced within 12 hr after exposure to 4.5 and 8.0 µM of compound **31** for Nalm06 and SEM respectively (Fig. 7). The data suggests that compound **31**-induced apoptosis in ALL cell models via the caspase-3-dependent pathway.

For Nalm06, caspase 3 activation was captured at the 12 hr time point (cleaved caspase 3, 17 kDa) while the positive control, staurosporine (0.5 µM) shows caspase-3 activation by the 3 hr time point.

Active caspase-7 is observed at the 6 hr time point, albeit at very low expression levels, but by the 12 hr time point, it can be clearly detected. No cleaved PARP (89 kDa) was detected between 3-6 hr treatment, but it was observed after 12 hr treatment. In terms of cleaved PARP, the positive control showed its presence at 3, 6 hr treatment, but at the 12 hr point no more PARP was detected.

For the SEM cell line, caspase 3 activation was observed at the 6 hr time point as well as the positive control. Active caspase-7 was also observed at the 6 hr and 12 hr time point. Cleaved PARP (89 kDa) was detected at the 3, 6, and 12 hr time point. No uncleaved PARP was observed at the 12 hr point. Next, we investigated effects of **31** on MAPKs in Nalm06 and SEM cell lines by immunoblot analysis. As shown in Fig. 7, compound **31** at concentration of 4.5 μM for Nalm06 and 8.0 μM for SEM respectively.

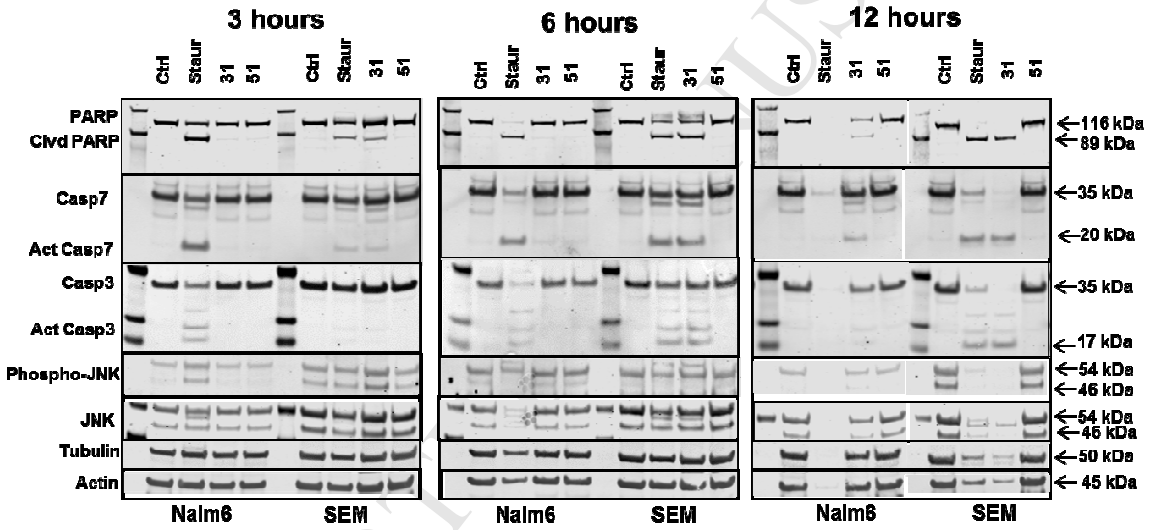

Figure 7. Western Blot of Nalm06, SEM for 3, 6, 12 hr respectively.

Compound **31** induced higher levels of phosphorylated JNK in SEM cells, but not in the Nalm06 cell line, presumably due to different mechanisms regulating apoptosis. JNK activation was increased through the time points for the positive control in the SEM, but not detected for Nalm06. These results indicate that JNK is involved in the mode of action of compound **31** in SEM cell lines, but not in Nalm06. A graphical quantification of JNK expressed as a ratio of Phospho JNK over total JNK normalized to the DMSO (control set to 1.0) is shown in Fig. 8 (signal intensities in color are included in SI).

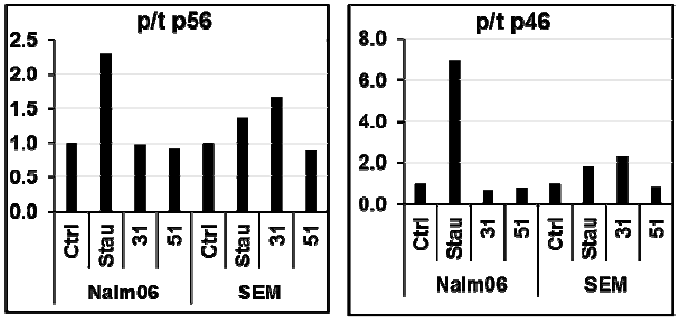

Figure 8. Phospho-JNK and total JNK (p/t) calculated as a measure of JNK activation.

Conclusions

In conclusion, the present study describes the synthesis and biological evaluation of the derivatives of the natural product BA against leukemia cellular models. It is well established that apoptosis and its associated signaling pathways can be targeted as potential therapies against malignancies, including infant ALL. We have identified lead compound **31** against B cell ALL models with promising potency (EC_{50}≤8 μM in Nalm06/SEM cells) and minimal cytotoxicity observed in HEPG2/BJ/Hek293 mammalian cell lines. Our results showed apoptosis induction in these ALL cellular models upon treatment with compound **31**. PARP cleavage and active caspase 3 increase levels suggested that the apoptotic program is caspase dependent. This monoterpene derivative provides a new lead molecular scaffold for further mechanistic studies to identify potential biological target(s) in ALL. The described experimental observations, growth inhibition, S phase arrest and caspase mediated apoptotic death in these leukemia B cell models induced by compound **31** warrant further mechanistic studies, which will be presented in due time.

Supplementary Data. Full details of the derivative syntheses and biological experimental methods are provided online at:

Competing interests. The authors declare that they have no competing interests.

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Highlights

- A focused-compound library based on the monoterpene, bakuchiol was synthesized.
- Compound **31** was identified as a potential lead against leukemia
- Compound **31** induces caspase-3 dependent apoptotic pathway