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Research paper

Anti-proliferative evaluation of monoterpene derivatives against leukemia

Lekh Nath Gautam, Taotao Ling, Walter Lang, Fatima Rivas*

Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, TN 38105-3678, USA

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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.

1. 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.

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,

* Corresponding author. Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, 262 Danny Thomas Place Memphis, TN 38105-3678, USA.
E-mail address: Fatima.rivas@stjude.org (F. Rivas).

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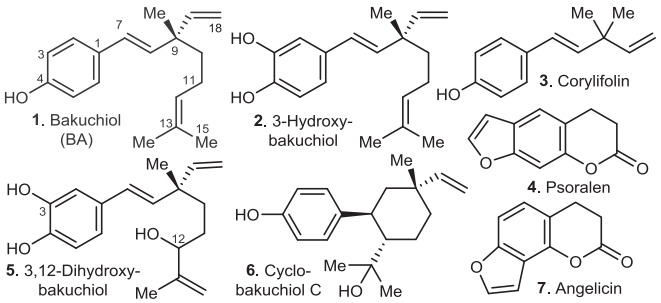

Fig. 1. Constituents of Psoralea corylifolia and related natural products.

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).

2. 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).

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).

Furthermore, compound **1** was evaluated under the Heck-Matsuda reaction (Figs. 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 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, and K_2CO_3 in DMF. The reaction was carried out under microwave conditions to afford compound **51**–**57** (Fig. 4) in modest to good yields (70–80%).

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

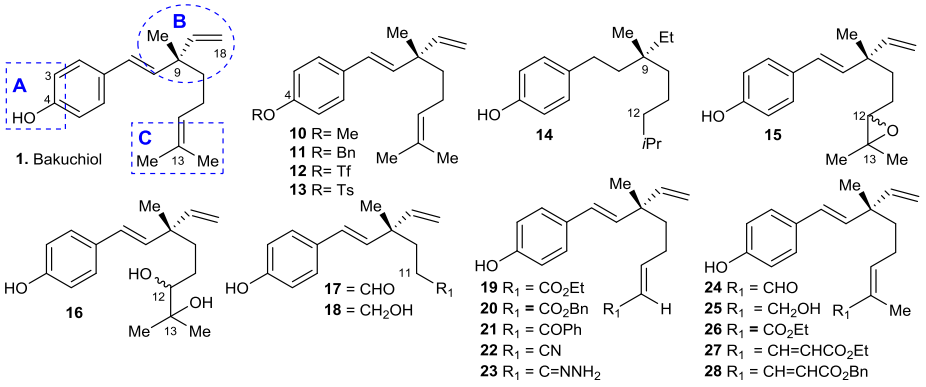

Fig. 2. BA derivatives at C4 and C11–C12.