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Novel compounds that target lipoprotein lipase and mediate growth arrest in acute lymphoblastic leukemia

Rajesh R. Nair [a,e], Werner J. Geldenhuys [b,e], Debbie Piktel [c], Prabodh Sadana [d], Laura F. Gibson [a,c,*]

[a] Department of Microbiology, Immunology and Cell Biology, School of Medicine, West Virginia University, Morgantown, WV 26506, USA
[b] Department of Pharmaceutical Sciences, School of Pharmacy, West Virginia University, Morgantown, WV 26506, USA
[c] West Virginia University Cancer Institute, West Virginia University, Morgantown, WV 26506, USA
[d] Department of Pharmaceutical Sciences, College of Pharmacy, Northeast Ohio Medical University, Rootstown, OH 44272, USA

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ABSTRACT

Over the past decade, the therapeutic strategies employed to treat B-precursor acute lymphoblastic leukemia (ALL) have been progressively successful in treating the disease. Unfortunately, the treatment associated dyslipidemia, either acute or chronic, is very prevalent and a cause for decreased quality of life in the surviving patients. To overcome this hurdle, we tested a series of cylopropanecarboxamides, a family demonstrated to target lipid metabolism, for their anti-leukemic activity in ALL. Several of the compounds tested showed anti-proliferative activity, with one, compound **22**, inhibiting both Philadelphia chromosome negative REH and Philadelphia chromosome positive SupB15 ALL cell division. The novel advantage of these compounds is the potential synergy with standard chemotherapeutic agents, while concomitantly blunting the emergence of dyslipidemia. Thus, the cylopropanecarboxamides represent a novel class of compounds that can be potentially used in combination with the present standard-of-care to limit treatment associated dyslipidemia in ALL patients.

B lineage acute lymphoblastic leukemia (ALL) is the most prevalent cancer diagnosed in pediatric patients. Fortunately, due to advances in treatment strategies approximately 90% of these patients will recover from the disease.[1,2] The etiology of the disease involves differentiation arrest followed by proliferation of the immature B cells leading to their accumulation within the bone marrow.[3] Proliferation is generally attributed to a fusion oncogene created by chromosomal translocation with BCR-ABL, called the Philadelphia chromosome, being studied the most.[4] At present, patients with ALL are typically treated with an induction dose followed by a consolidation therapy and finally the patients are kept on a maintenance therapy along with CNS prophylaxis, if specifically warranted, based on tumor phenotype.[5,6] However, with great success with treatment, obesity has been identified as an unanticipated potential long-term harmful effect of the cancer therapy in ALL survivors.[7,8] The cause of obesity has been attributed to treatment-induced alteration of altered cholesterol metabolism leading to elevated triglycerides and very-low-density lipoprotein (VLDL) and low levels of high-density lipoprotein (HDL).[9] Specifically, the hyperlipidemia during treatment with chemotherapy has been shown to be correlated with decreased lipoprotein lipase activity.[10] In light of this, the present study was undertaken to identify novel compounds that could target lipid metabolism pathway and be used in combination with chemotherapy to curb the obesity effect of therapy in ALL.

Recently we identified a series of cyclopropanecarboxamides that modulate lipid metabolism *in vivo*.[11–13] These compounds shared a common fluorinated carboxamide moiety with the R-groups studied for structure-activity relationships. One of these compounds, the lead structure (Fig. 1), was found to be a modulator of triglyceride metabolism. Since it has been shown that dysregulated lipid metabolism may be a key factor in the causation of obesity in ALL survivors,[14] we screened the cyclopropanecarboxamides for potential leads in an ALL drug discovery program.

We screened a series of cyclopropanecarboxamides in two different ALL cell lines, including Philadelphia chromosome negative cell line, REH (peripheral blood derived) and Philadelphia chromosome positive, SupB15, (bone marrow derived) (Fig. 2). Because, the oncogenes driving proliferation are different in both cell lines, with BCR-ABL oncogene driving proliferation of SupB15 and TEL-

* Corresponding author at: 1 Medical Center Drive, West Virginia University, Morgantown, WV 26506 USA.
E-mail address: lgibson@hsc.wvu.edu (L.F. Gibson).
[e] Equal first author contribution.

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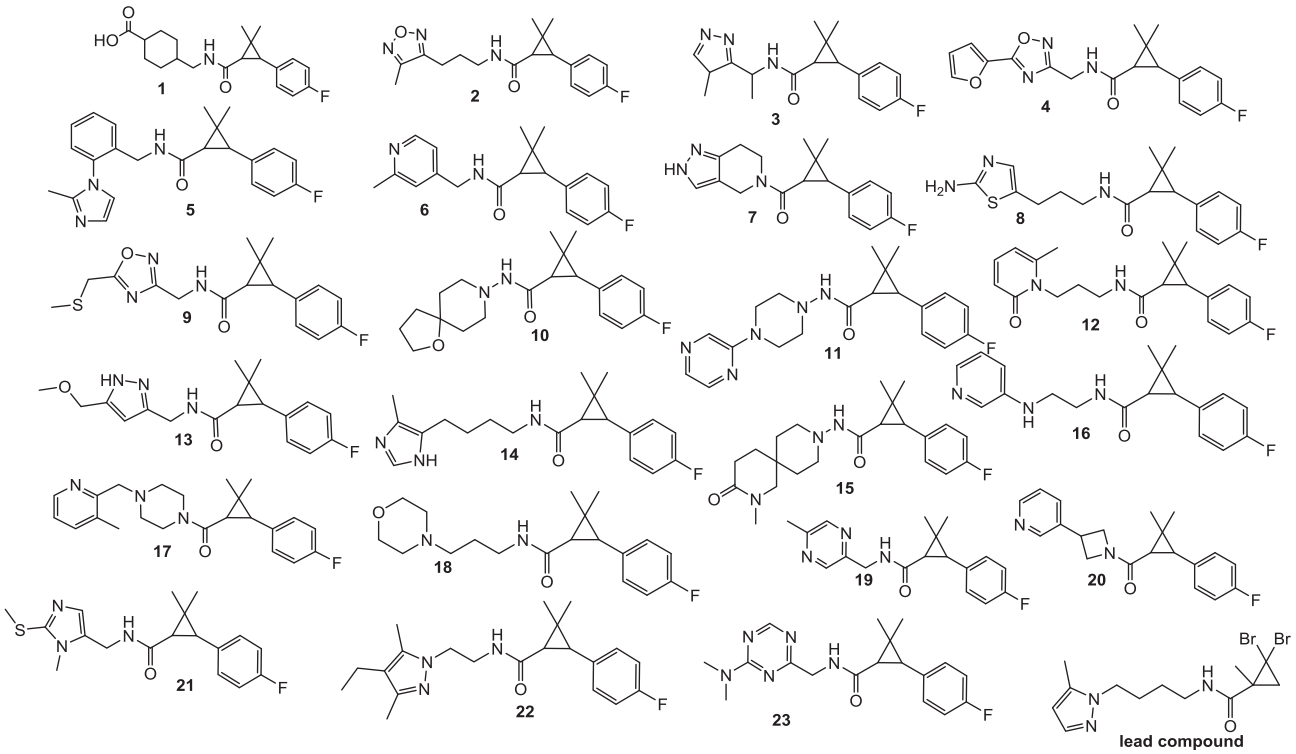

Fig. 1. Structures of the compounds tested in the B-cell ALL cells.

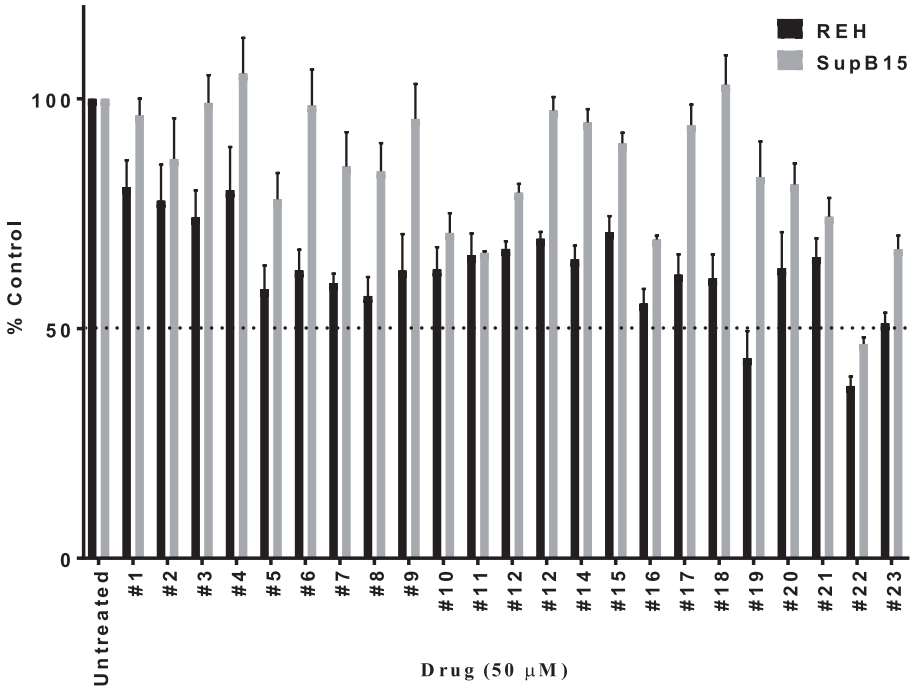

Fig. 2. Results from the cell proliferation screening assay of the compounds in the REH and SupB15 ALL cells. Each bar represents mean ± SEM where N = 3.

AML1 oncogene driving proliferation of REH, it is critical to identify novel compounds that are effective in these diverse cell phenotypes. The physico-chemical properties of the tested compounds are shown in Table 1. All compounds were obtained from the Chembridge Chemical company (www.hit2lead.com).

Fig. 2 shows the results of the screen. Both types of cells were grown in 96-well plates at a density of 50,000 cells per well. Cells were treated with the compounds at final concentration (50 μM), and the cell proliferation was tested after 72 h of incubation with the compounds. A cell counting kit was utilized according to the