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Short communication

Synthesis and evaluation of the cytotoxic activity of novel ethyl 4-[4-(4-substitutedpiperidin-1-yl)]benzyl-phenylpyrrolo[1,2-*a*]quinoxaline-carboxylate derivatives in myeloid and lymphoid leukemia cell lines

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ABSTRACT

Leukemia is the most common blood cancer, and its development starts at diverse points, leading to distinct subtypes that respond differently to therapy. This heterogeneity is rarely taken into account in therapies, so it is still essential to look for new specific drugs for leukemia subtypes or even for therapy-resistant cases. Among heterocyclic compounds that attracted a lot of attention because of its wide spread biological activities, the pyrrolo[1,2-*a*]quinoxaline heterocyclic framework has been identified as interesting scaffolds for antiproliferative activity against various human cancer cell lines. In the present study, novel ethyl 4-[4-(4-substitutedpiperidin-1-yl)]benzyl-phenylpyrrolo[1,2-*a*]quinoxaline-carboxylate derivatives **1a-l** have been designed and synthesized. Their cytotoxicities were evaluated against five different leukemia cell lines, including Jurkat and U266 (lymphoid cell lines), and K562, U937, HL60 (myeloid cell lines), as well as normal human peripheral blood mononuclear cells (PBMNCs). Then, apoptosis study was performed with the more interesting compounds. The new pyrrolo[1,2-*a*]quinoxaline series showed promising cytotoxic potential against all leukemia cell lines tested, and some compounds showed better results than the reference compound A6730. Some compounds, such as **1a**, **1e**, **1g** and **1h** are promising because of their high activity against leukemia and their low activity against normal hematopoietic cells. Structure-activity relationships of these new synthetic compounds **1a-l** are here also discussed.

1. Introduction

Acute leukemia is one of the most aggressive hematopoietic malignancies and is characterized by the abnormal proliferation of the immature cells and a premature block in lymphoid or myeloid differentiation. Adult acute leukemia have a poor prognosis due to a

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large number of relapses. Thus, identifying and understanding the treatment-related resistance mechanisms is of major interest to improve the therapeutic strategy [1]. Therefore, there is an urgent need to find new therapeutics, which could led to the development of novel treatment strategies with less or minimal side effects.

Heterocyclic compounds attracted a lot of attention because of its wide spread biological activities. Among them, the pyrrolo[1,2-*a*]quinoxaline heterocyclic framework constitutes the basis of an important class of compounds possessing interesting biological activities. These compounds have been reported to serve as key intermediates for the assembly of several heterocycles including antipsychotic agents [2], anti-HIV agents [3], adenosine A_3 receptor modulators [4], antiparasitic agents [5–10], and antitumor agents [11–13]. In this last field, the discovery and development of novel therapeutic agents are one of the most important goals in medicinal chemistry. In this context, we have recently published three series (Series **A-C**) of new interesting substituted pyrrolo[1,2-*a*]quinoxalines (Fig. 1) endowed with good activity towards the human leukemia cells [14–16]. These antiproliferative pyrrolo[1,2-*a*]quinoxaline derivatives have been previously designed as novel structural analogues of compound A6730, a well-described Akt inhibitor that presents antiproliferative activity against different human leukemia cell lines [14–17]. Continuing our efforts in this field and considering the pharmacological activities of pyrroloquinoxalines on human leukemic cells, a new series (Series **D**) was designed and synthesized. Thus, by taking into accounts the best results obtained in series **B** (Fig. 1), we decided to use the JG576 and JG572 pyrrolo[1,2-*a*]quinoxaline moieties as a template for the design of new derivatives **1a-l** in which the pyrrole nucleus is substituted in different positions by a phenyl and an ester function (Series **D**, Fig. 1). In relation to our previous works, further pharmacomodulations on the piperidine core have been considered, such as the introduction of new substituted heterocyclic systems [14–16]. The antiproliferative profile of the obtained derivatives **1a-l** was then evaluated *in vitro* against a panel of myeloid (U937, HL60, K562) or lymphoid (Jurkat, U266) leukemic cell lines. Moreover, to determine their respective cytotoxicity, the new ethyl 4-[4-(4-substitutedpiperidin-1-yl)]benzyl-phenylpyrrolo[1,2-*a*]quinoxaline-carboxylate derivatives **1a-l** were tested on activated human peripheral blood mononuclear cells, and assessment of apoptosis was performed with the more interesting compounds. Structure-activity relationships of these new synthetic compounds **1a-l** are here discussed. Finally, we used simple computational programs to predict the drug-like characteristics through the calculated

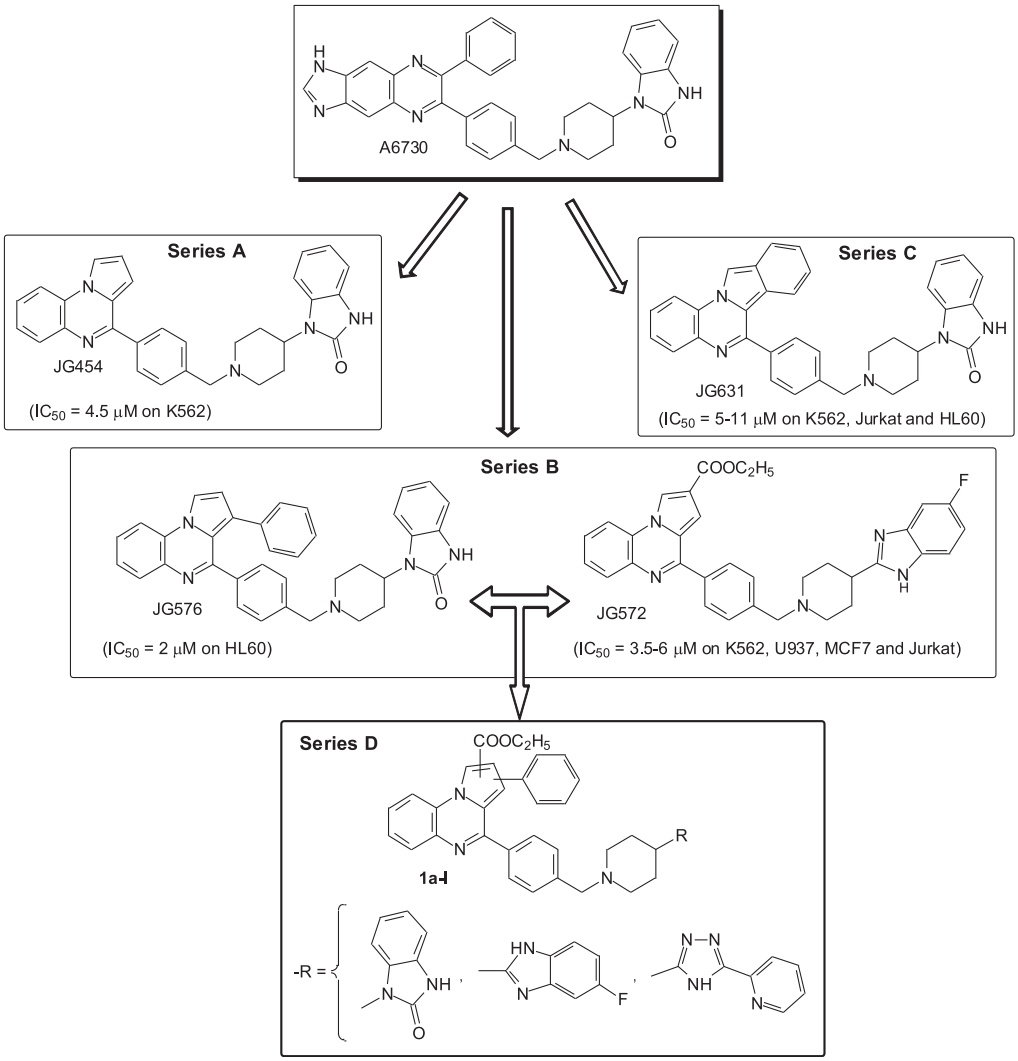

Fig. 1. Structure of bioactive compounds of previously described series A-C, and general structure of new synthesized substituted pyrrolo[1,2-*a*]quinoxaline derivatives **1a-l** (series D).