New benzimidazole-derived PI3Kδ inhibitors as highly potent drug candidates for SLE and other inflammatory and autoimmune diseases.

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INTRODUCTION

PI3K (Phosphoinositide 3-kinase) is the family of lipid kinases that participates in many key cellular processes like proliferation, growing up, migration, cytokines production, and apoptosis. These proteins are highly expressed in many human cells, such as leukocytes, which have implications for the body’s immune response. They are involved in metabolism regulation, normal embryogenesis, or maintaining glucose homeostasis. Inhibition of PI3K (especially the class I, which contains four subunits: α, β, γ, and δ) is regarded as being very attractive as a potential therapeutic method for treating many diseases such as SLE (Systemic Lupus Erythematosus), MS (Multiple Sclerosis), IBD (Inflammatory Bowel Disease) and other inflammatory and autoimmune diseases [1-4]. In this work, we present a series of new, very potent, active, ad selective small molecule inhibitors based on the structure of appropriately substituted 5-(2-difluoromethylbenzimidazo[1,1-a]pyrazolo[1,5-d]pyrimidine) [5] as highly potent drug candidates.

SYNTHESIS

In our research, it was reported that modifications of benzimidazoles groups and amine subunits play a crucial role in the activity and selectivity of PI3K inhibitors. We focused on the pyrazolo[1,5-d]pyrimidine core. It was investigated that there are two very important interactions. The first is the binding between the oxygen atom of the morpholine ring and VO₂⁻. The second bond is formed between the nitrogen atom at the third position of benzimidazole derivative (especially 2-(difluoromethyl)-1H-benzimidazole) and μ₃-η[79]. (Fig.1).

A new family of substituted pyrazolo[1,5-d]pyrimidines (Fig.2) was prepared in multi-step synthesis included the hydrolysis reaction, oxygenation reaction, or reductive amination. Compounds (Sa – S5) were obtained after four step synthesis from 5-chloro-7-(morpholin-4-yl)pyrazolo[1,5-d]pyrimidine-2-carboxamide. Compounds (Sa – S6) (replacement of the (CO) group in position no.2 of pyrazolo[1,5-d]pyrimidine derivatives) were prepared after three-step synthesis from the same substrate (Scheme 2).

RESULTS

In our work, we synthesized a library of very active benzimidazole derivatives [PI3Kδ IC₅₀ = 0.02 – 0.80 μM]. Many substituted pyrazolo[1,5-d]pyrimidines were prepared with different amine groups in multi-step synthesis. Then we developed the process of lead compounds synthesis to select the preclinical candidate for SLE. Molecular modeling studies explain the interaction of active structures in the PI3Kδ ATP binding site. Pyrazolo[1,5-d]pyrimidine in morpholine at position 7, 2-(difluoromethyl)benzimidazole at position 5 and tert-butylamine as amine proved to be the most potent structure (IC₅₀ = 18 nm). Moreover, this structure shows good selectivity to other PI3K (isofoms PI3Ka/PI3Kβ = 79; PI3Kδ/PI3Kβ = 939) and promising biological properties. The lead compound (CPL024A15) (Fig.3) is subjected to further biological, toxicological, and pharmacokinetic studies.

CONCLUSIONS

The library of active compounds was obtained. It was observed that the most promising are piperazine- and piperidine- derivatives (position 2) (Fig.2). Compounds with satisfactory parameters were selected from the entire library. Nine final structures with an IC₅₀ value of less than 100 nM were obtained (Tab.1). The most promising compound (CPL024A15) is 1-[2-[[4-(tert-butyl)piperazin- 1-yl]methyl]-7-(morpholin-4-yl)pyrazolo[1,5-d]pyrimidine-5-yl]-2-(difluoromethyl)-1H-benzimidazole (Fig.3) with potent activity (IC₅₀ = 18 nm), selectivity (PI3Ka/PI3Kβ = 79; PI3Kδ/PI3Kβ = 939) and promising other parameters (Tab.2).

Table 1. Observed PI3K inhibitors – pyrazolo[1,5-d]pyrimidine derivatives; n/a = data not available.

Table 2. CPL024A15 parameters; *: KINETIC pH 7.4.

REFERENCES