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Synthesis of Quinazoline Derivatives for Adenosine Kinase Inhibition

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Abstract

The project consists in the development of three anilinoquinazoline synthetic derivatives (3-bromoanilinoquinazoline, 4-iodoanilinoquinazoline and 4-acetateanilinoquinazoline), by simple synthesis methods – ciclization, halogenation and eletrophilic aromatic substitution – with aplication on adenosine kinase (ADK) inhibition, which is linked with the prevention of many diseases, such as infarct, stroke and others.

Key words:

Quinazoline, Adenosine Kinase, Enzyme Inhibition.

Introduction

Due to the huge pharmacological interest related to adenosine kinase (ADK) enzyme, new heterocyclic compounds have been studied in the last decades with the intent of producing new drugs that could act as interesting ADK inhibitors. In this context, the anilinoquinazoline derivatives manifest a great potential for inhibition for new therapeutic approaches, being possible to obtain them through a short synthetic route that starts from a simple aromatic compound.

Even though some ADK inhibitors are already known and used for some treatments, some disadvantages affect their efficiency, such as low bioavailability, low half-life time, low selectivity and, often, toxicity. Because of that, the development of new ADK inhibitors is rather important from the pharmacological point of view.

Therefore, quinazoline derivatives such as anilinoquinazoline derivatives have a great pharmacological potential; they are not only of simple obtainment, but they also present a great number of possible variations and chemical modifications, resulting in a wide array of drug candidates.

Results and Discussion

The synthetic route is based in three main steps: A) cyclization, B) halogenation (chlorination) and C) eletrophilic aromatic substitution. The synthetic route is outlined in image 1.

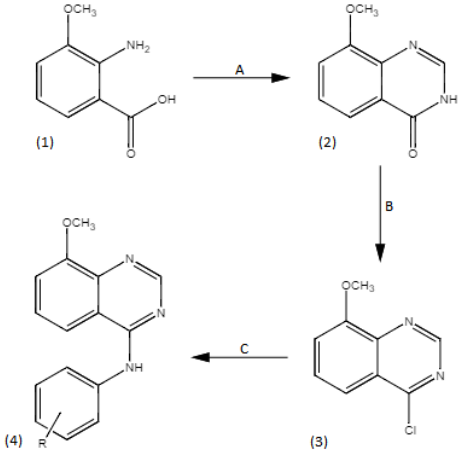

Figure 1. Synthetic route of a anilinoquinazoline derivatives synthesis: *(A) formamidine acetate, 110 ºC for 5 h, (B) thionyl chloride, DMF$_{(cat.)}$, 85 ºC for 2 h, (C) aniline derivative, isopropanol, 110 ºC for 2 h.*

Step A) consisted in the reaction involving 2-amine-3-metoxibenzoic acid (1) with formamidine acetate, which leads to cyclization, producing the quinazolinone (2). This step had 83% yield.

Step B) At inert atmosphere, the obtained quinazolinone was chlorinated using thionyl chloride and dimetilformamide (DMF) as reaction catalyst, generating an orange yellow product, that contains the 4-clhorinequinazoline (3).

Step C) The product from Step B was purified by extraction steps, resulting in pure 4-chloro-8-methoxy-quinazoline, which was combined with isopropanol and aniline derivatives, generating the bromine, iodide and acetate derivatives of anilinoquinazoline inhibitors, which are presented in Figure 2. This step had 20-99% yield.

Each synthesis step was monitored through thin-layer chromatography, and the products were analyzed aplying Nuclear Magnetic Resonance (NMR) Spectroscopy and Fourier-Transformed Infrared Spectroscopy (FTIR), in order to confirm the success of each step.

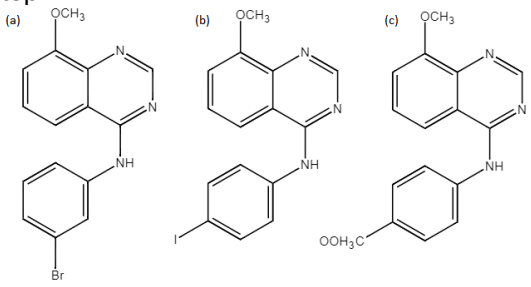

Figure 2. Synthetic inhibitors of ADK enzyme. *(a) bromide, (b) iodide and (c) acetate anilinoquinazoline derivatives*.

Conclusions

4-Anilinoquinazoline derivatives were synthesized in a 3-step synthetic route as confirmed by NMR and FTIR spectroscopic techniques. Thus, these compounds can be utilized in the near future for studies involving inhibition assays with the adenosine kinase enzyme.

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