Synthesis of novel carboxamides derived from 6-sulfonamide-4-oxoquinoline as potential cholinesterase inhibitors

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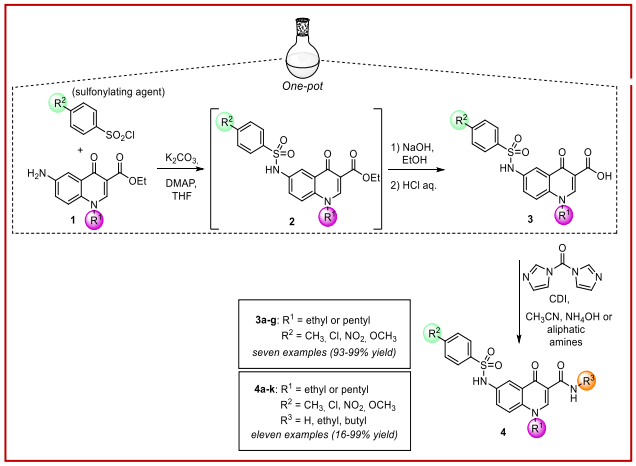
Introduction

Alzheimer's Disease (AD) is the sixth leading cause of death in the world and mainly affects the elderly. Among the main factors responsible for the onset of AD is the low concentration of the neurotransmitter acetylcholine (ACh) present in the Central Nervous System, Peripheral Nervous System and neuromuscular junctions.[1] Low levels of ACh result from increased hydrolytic activity promoted by the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) to convert ACh into choline and acetate.[2] Studies indicate that the 4-oxoquinoline scaffold and the carboxamide and sulfonamide functional groups are present in different substances capable of regulating the cholinergic deficit through the inhibition of cholinesterase.[3,4] Therefore, in this work is being described the synthesis of 6-sulfonamide-4-oxoquinoline-3-carboxamides as potential cholinesterase inhibitors.

Results and Discussion

6-sulfonamide-4-oxoquinoline-3-carboxamides (**4**) were synthesized from 6-amino-4-oxoquinoline **1** by a one pot reaction involving sulfonylation and alkaline hydrolysis, in sequence.



Scheme 1 – Synthetic route used for preparing 6-sulfonamide-4-oxoquinoline-3-carboxamides **4a-k**.

Carboxylic acid intermediates (**3**) were then reacted with ammonia or aliphatic amines, in the presence of 1,1'-carbonyldiimidazole (CDI) as a coupling reagent, providing carboxamides **4**, (Scheme 1) without the need for further purification steps.

Altogether, seven new 6-sulfonamide-4-oxoquinoline-3-carboxylic acid derivatives (**3**) were synthesized with yields of 93-99% and eleven 6-sulfonamide-4-oxoquinoline-3-carboxamide (**4**) with yields in the range of 16-99%. These substances will also be submitted to biological tests to evaluate their possible anticholinesterase action.

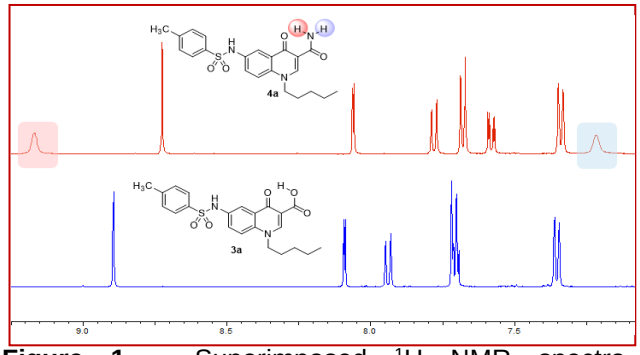


Figure 1 – Superimposed ^{1}H NMR spectra (500MHz, DMSO-d_6) of compounds **3a** and **4a**.

Conclusions

The methodology used to obtain 6-sulfonamide-4-oxoquinoline-3-carboxamides **4** proved to be efficient, making it possible to obtain a series of eleven (**4a-k**) substances in moderate to excellent yields. Furthermore, seven new 6-sulfonamide-4-oxoquinoline-3-carboxylic acids (**3a-g**) were obtained in excellent yields. The synthesized substances will be evaluated in enzyme inhibition assays in collaboration with Prof. Dr. Marcela Cristina de Moraes (UFF).

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[1] Alzheimer'sDement. 2021, 17, 327–406.
[2] Roger M. Lane, Steven G. Potkin, Albert Enz. International Journal of Neuropsychopharmacology. 2006, 9, 101–124.
[3] Muhammad Mansha; Muhammad Taha; El Hassane Anoua; Nisar Ullah. Arabian Journal of Chemistry. 2021, 14, 7, 103211.
[4] M.Hassan, M. A. Abbasi, A. Rehman, S. Z. Siddiqui, G. Hussain, S. A. A. Shahc, M. Shahidd, S. Seo. Journal of Theoretical Biology. 2018, 458, 169–183.