Studies toward an indanone-based hybrid with potential AchE inhibition to treat Alzheimer’s disease

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Keywords: Alzheimer disease, acetylcholinesterase inhibitor, synthesis intermediate

INTRODUCTION

The Alzheimer’s disease (AD) is a process that causes a progressive and irreversible decline of cognitive functions, which includes no organized behavior and psychotic symptoms. The progression of the disease symptoms is associated with structural changes in cholinergic synapses in certain brain regions and consequent impairment of cholinergic neurotransmission[5,6].

The AD is complex, and nowadays the therapeutic treatment offers only limited and few benefits for the patients, so it is essential to search for alternative AD treatments. In this work, we summarize the synthesis of (4-piperidin-1-yl)-[4-azidequinolin-2-yl]-methyl alcohol (8), as key intermediate to synthesize indanone-based hybrid (1) with potential acetylcholinesterase inhibiton (Fig. 1) and to treat AD.

![Figure 1. Indianone-based hybrid (1) as potential inhibitor of acetylcholinesterase.](image)

RESULTS AND DISCUSSION

As seen on scheme 1 (entry i), the treatment of antranilic acid (2) with POCl₃ and acetone afforded the chloride-quinoline derivative (3) (40% yield) [3]. The methyl group of 3 was oxidized with SeO₂ and TBHP (tret -butyl hidroperoxide) to give 4-chloropiperidinyl carbaldehyde (4) (62 % yield) [4]. In entry (ii) ethyl isonepeptate (5) (commercial) was reduced to the 4-piperidylmethanol (6) in the presence of LiAlH₄ in anhydrous THF (90% yield) [5].

The next step (entry iii) the synthesis of compound 7 was achieved by a reductive amination between the aldehyde 4 and piperidine derivative 6 in sodium triacetoxoborohydride (NaBH(OAc)₃) and 1,2 dichloroethane (65% yield) [8]. After that, the chloride atom of 7 was replaced by azide using NaN₃ in DMF, which gave the key intermediate (4-piperidin-1-yl)-[4-azidequinolin-2-yl]-methyl] methyl alcohol (82% yield) (8) (Scheme 1)[7].

CONCLUSION

We have performed the preparation of the key intermediate 4-piperidin-1-yl-[4-azidequinolin-2-yl]methyl] methyl alcohol (8) of a total synthesis of a potential AchE inhibitor (1). The next steps involves the condensation between the aldehyde derivative (9), obtained from oxidation of (8), with commercial 5,6 dimethoxy-1-indanone (10). The double bond formed of 11 will be reduced in parallel to the azide function in one pot reaction to achieve the desired compound 1, as shown before.

ACKNOWLEDGEMENTS

University of São Paulo, Faculty of Pharmaceutical Sciences of Ribeirão Preto, and Fapesp for the Financial support.

REFERENCES