Studies toward an indanone-based hybrid with potencial AchE inhibition to treat Alzheimer's disease

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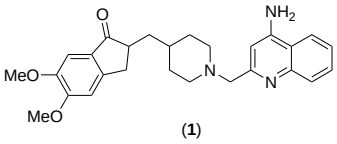
INTRODUCTION

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[1, 2].

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] methyl alcohol (**8**), as key intermediate to synthesize indanone-based hybrid (**1**) with potencial acetylcholinesterase inhibiton (Fig. 1) and to treat AD.

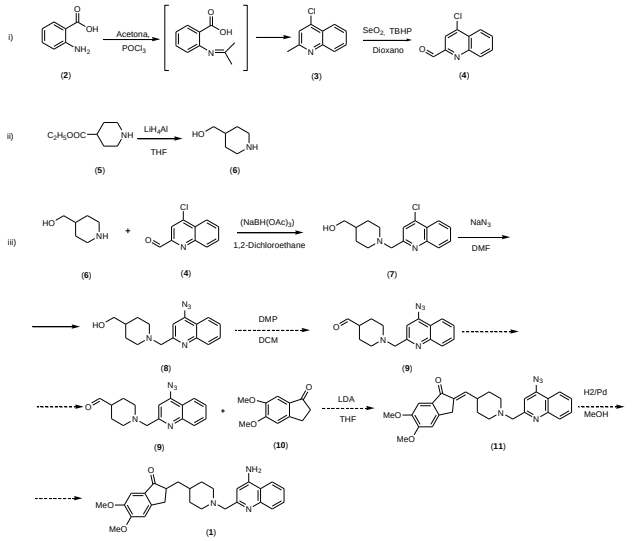


(**1**)

Figure 1. Indanone-based hybrid (**1**) as potencial inhibitor of acetylcholinesterase.

RESULTS AND DISCUSSION

As seen on scheme 1 (entry i), the treatment of antranilic acid (**2**) with $POCl_3$ and acetone afforded the chloride-quinoline derivative (**3**) (40% yield) [3]. The methyl group of **3** was oxidized with SeO_2 and TBHP (tert -butyl hidroperoxide) to give 4-chloro-piperidinyl carbaldehyde (**4**) (62 % yield) [4]. In entry (ii) ethyl isonepecotate (**5**) (commercial) was reduced to the 4-piperidylmethanol (**6**) in the presence of $LiAlH_4$ 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 triacetoxyborohydride ($NaBH(OAc)_3$) and 1,2 dichloroethane (65% yield) [6]. After that, the chloride atom of **7** was replaced by azide using NaN_3 in DMF, which gave the key intermediate (4-piperidin-1-yl)-[(4-azidequinolin-2-yl)-methyl] methyl alcohol (82% yield) (**8**) (Scheme 1) [7].



Scheme 1. Synthesis of the intermediate (4-piperidin-1-yl)-[(4-azidequinolin-2-yl)-methyl] methyl alcohol (**8**) of a total synthesis of a potencial AchE inhibitor (**1**).

CONCLUSION

We have performed the preparation of the key intermediate 4-piperidin-1yl-[(4-azidequinolin-2-yl) methyl] methyl alcohol (**8**) of the total synthesis of a potencial 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.

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REFERENCES

[1] Rev.**Bras.Psiquiatr**. vol.21, s.2, Oct. 1999.
[2] Journal of Molecular Graphics and Modelling v. 25, p. 169-175, 2006.
[3] Bioorg. Med. Chem.,18. p. 5995-6005, 2010.
[4] Heterocycles v.60, n.4, p.953-957.
[5] Eur. J.Org. Chem, p.4277-4295, 2008.
[6] J.Org.Chem.v.61, p. 3849-3862, 1996.
[7] Química nova, v.29, n.3, p.444-51, 2006.