Synthesis of tacrine-lophine hybrids

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INTRODUCTION

Our research group has been involved in the development of cholinesterases (ChEs) inhibitors as potential drugs of Alzheimer’s disease (AD).¹ Tacrine (1) was the first approved ChEs inhibitor by the FDA for the treatment of AD, although its side effects, the search for tacrine hybrids is very important. The bis(7)-tacrine analogues linked by an alkylene chain (bis(n)-cognitin) were prepared and it was proved that these dimeric molecules of tacrine offered a much stronger potency. As part of our studies directed towards the synthesis and biological screening for compounds with ChEs inhibitory activity, we describe herein or studies on the synthesis of a new series of tacrine-lophine hybrids linked by an alkylene chain.²

RESULTS AND DISCUSSION

Tacrine-lophine hybrids linked by an alkylene chain were prepared as described in Scheme 1. Compounds 4 were synthesized using a previously reported method.² The one-pot four-component reaction of 4, aldehydes 5, benzils 6 and NH₄OAc (7) was carried out in the presence of several Lewis to produce the respective hybrids 3a-g. InCl₃ was found as the best catalyst for these reactions. All reactions were performed in refluxing EtOH for 96h.

In Table 1 are presented some examples of tacrine-lophine hybrids linked by an alkylene chain. We also synthesized the hybrids bis(7)-lophine and bis(7)-tacrine in order to subject to the ChEs inhibitory activity studies.

CONCLUSION

In summary, we have developed an important four-component one-pot condensation synthesis of tacrine-lophine hybrids. The AChE and BuChE biological screening of several new compounds are currently underway.

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REFERENCES