

Synthesis of tacrine-lophine hybrids

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Keywords: Synthesis, Tacrine, Lophine

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 our studies on the synthesis of a new series of tacrine-lophine hybrids linked by an alkylene chain.²

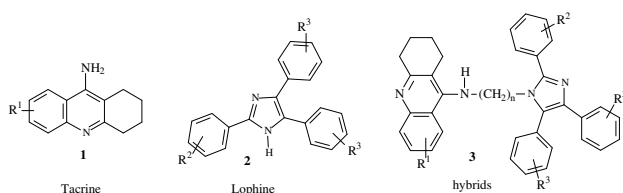
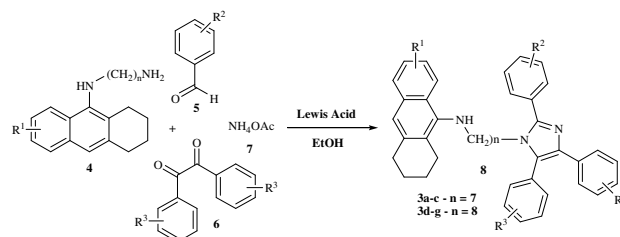


Figure1. Tacrine, Lophine and tacrine-lophine hybrid.

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 acids 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.



Scheme 1. Synthesis of Tacrine-Lophine hybrids

Table 1. Tacrine-Lophine hybrids.

Entry	R ²	(CH ₂) _n	Yield ^{a,b} (%)
1	<i>p</i> -Cl	7	3a - 33
2	<i>p</i> -NO ₂	7	3b - 54
3	<i>p</i> -OMe	7	3c - 54
4	<i>p</i> -Cl	8	3d - 57
5	<i>p</i> -NO ₂	8	3e - 39
6	<i>p</i> -CN	8	3f - 33
7	<i>p</i> -OMe	8	3g - 74

^a) Reaction were performed using InCl₃ (0.15 equiv.)

^b) After purification by flash chromatography..

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.

ACKNOWLEDGEMENTS

CNPq, FAPERGS and PROPESQ-UFRGS

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