LUPANE TRITERPENOIDS, SELECTIVE BUTYRYLCHOLINESTERASE INHIBITORS

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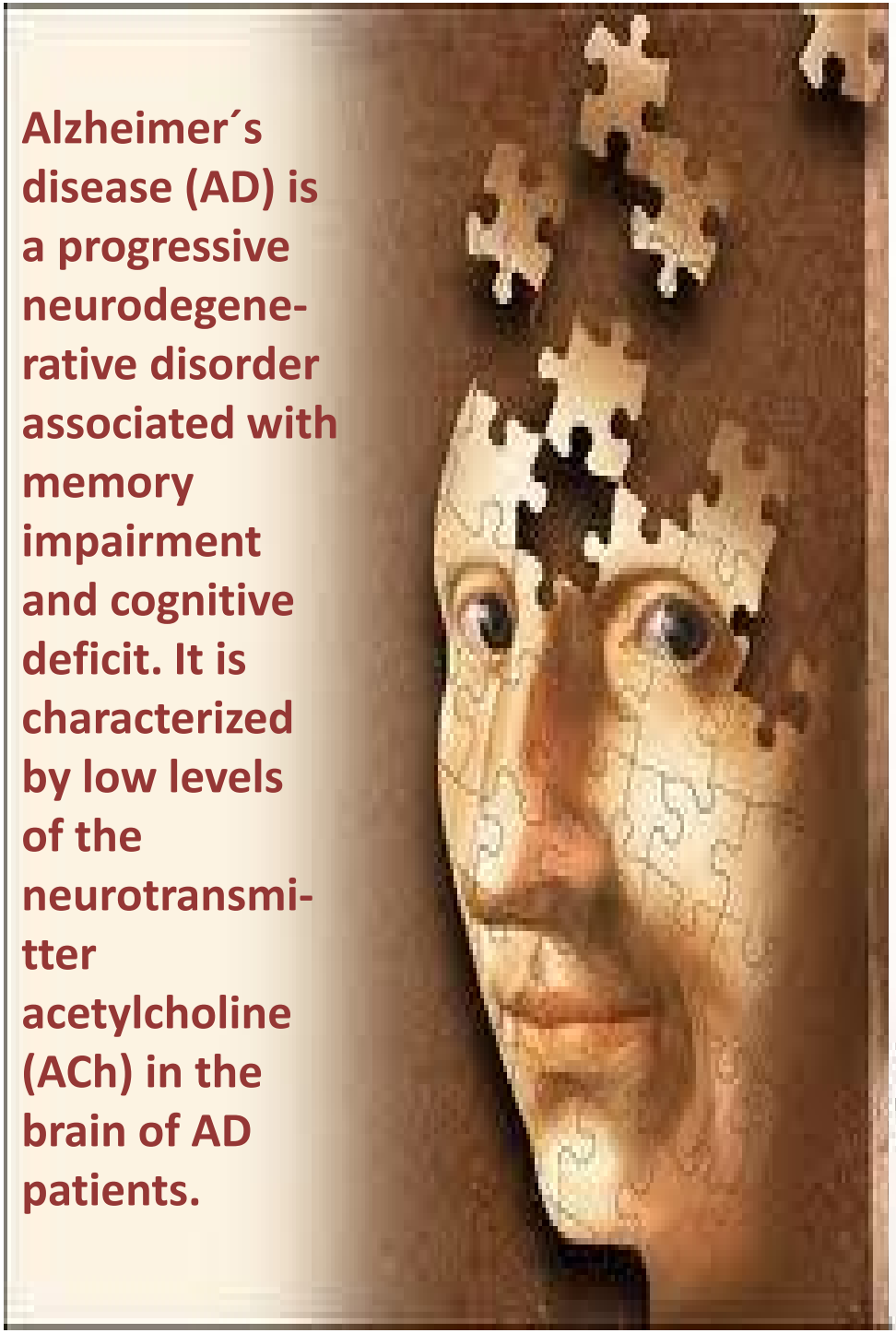
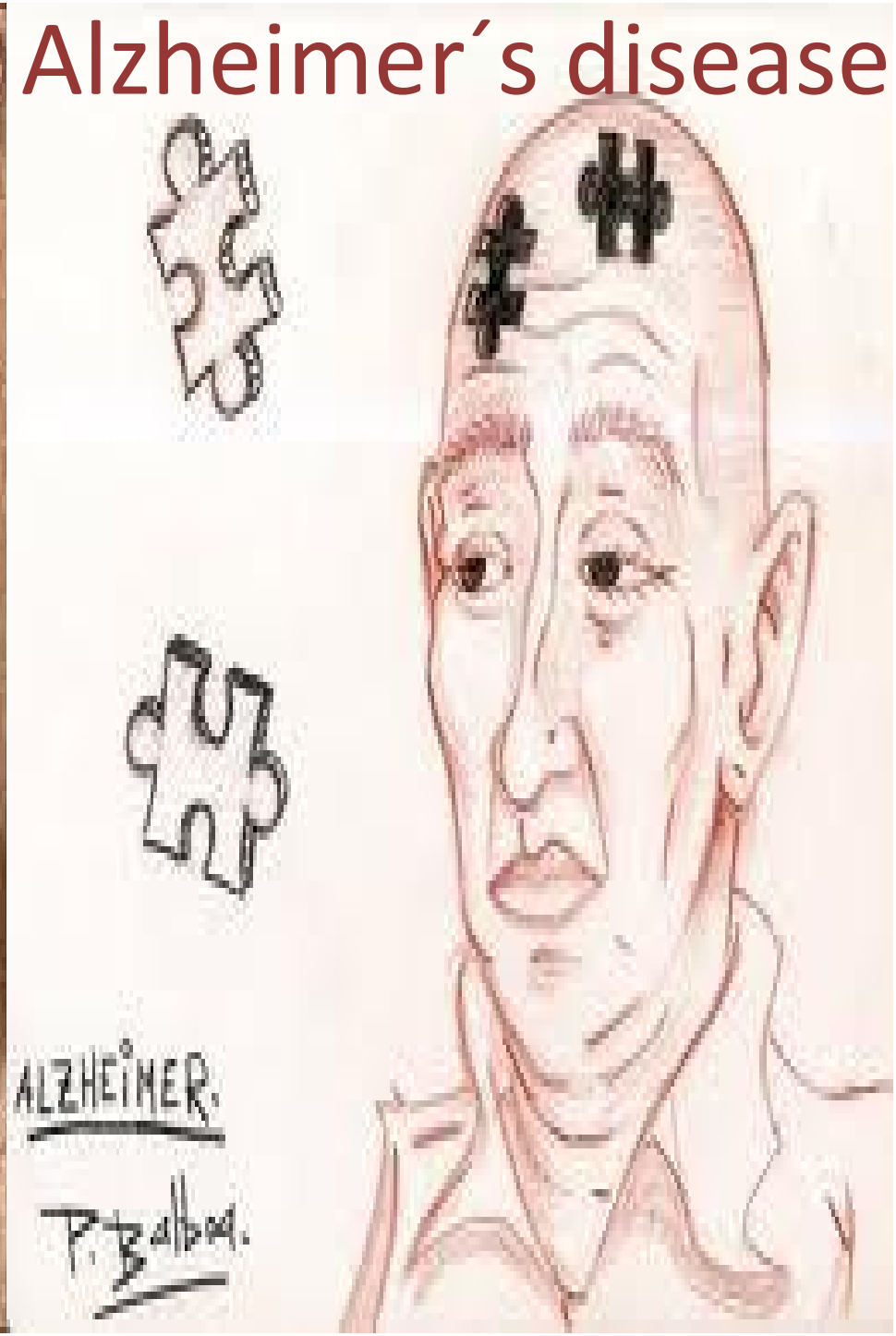
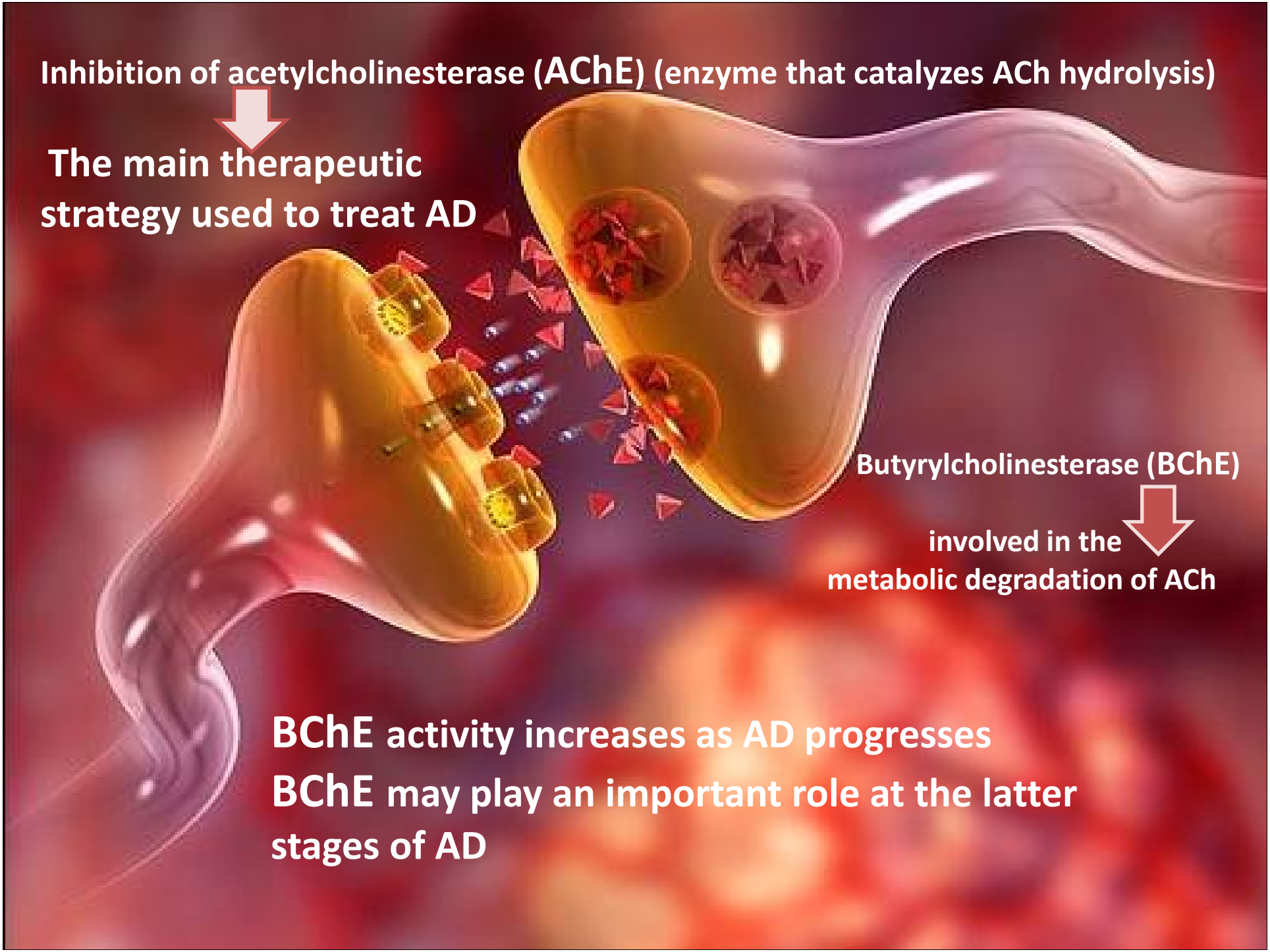
Alzheimer´s disease

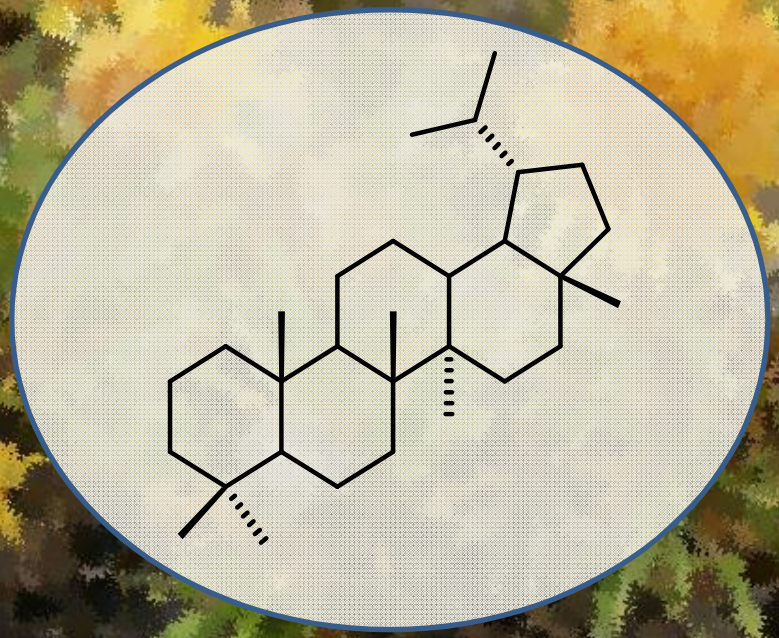
Alzheimer´s disease (AD) is a progressive neurodegene-rative disorder associated with memory impairment and cognitive deficit. It is characterized by low levels of the neurotransmi-tter acetylcholine (ACh) in the brain of AD patients.





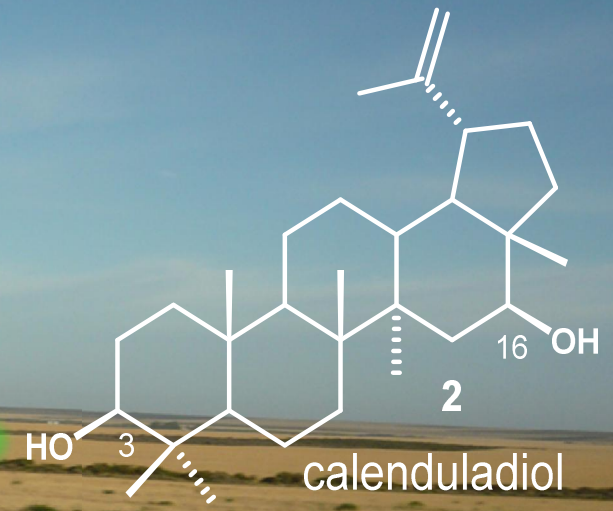

Inhibition of acetylcholinesterase (AChE) (enzyme that catalyzes ACh hydrolysis)
The main therapeutic strategy used to treat AD
Butyrylcholinesterase (BChE)
involved in the metabolic degradation of ACh
BChE activity increases as AD progresses
BChE may play an important role at the latter stages of AD

The chemistry of lupane-type triterpenoids has been actively explored due to their biological and pharmacological properties. Abundant in many plants, these metabolites are valuable natural raw materials to perform chemical modifications.

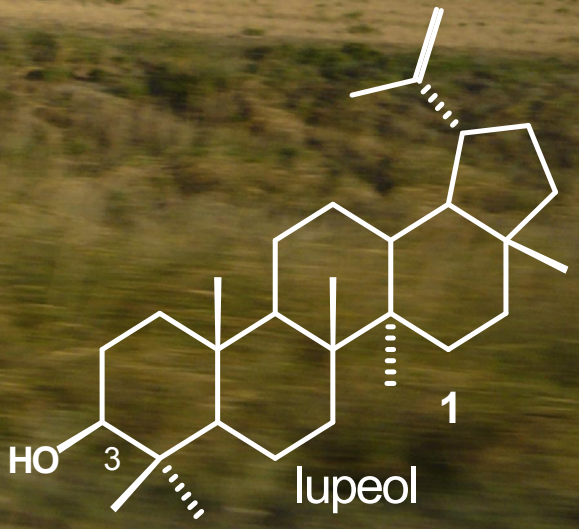


In the present work, we aimed to evaluate of natural and semisynthetic lupanes as potential *in vitro* cholinesterase inhibitors

Lupeol (1) and calenduladiol (2) have been isolated from *Chuquiraga erinacea* subsp. *erinacea* (Asteraceae), an endemic species growing wildly in our region

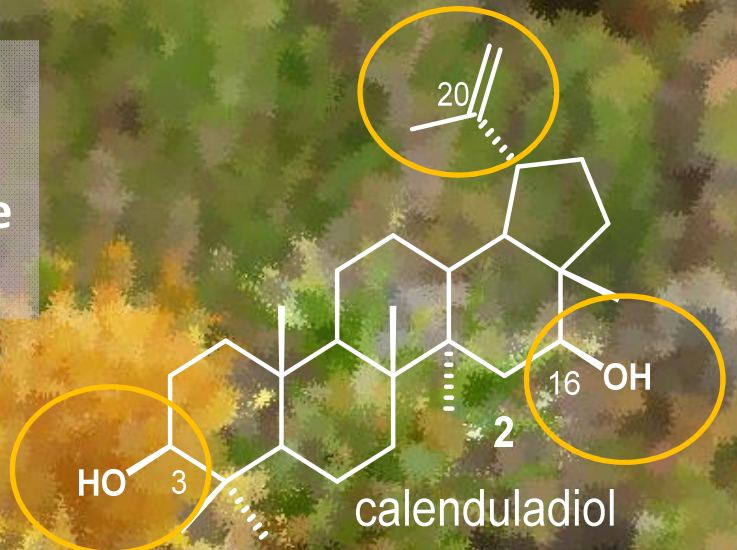


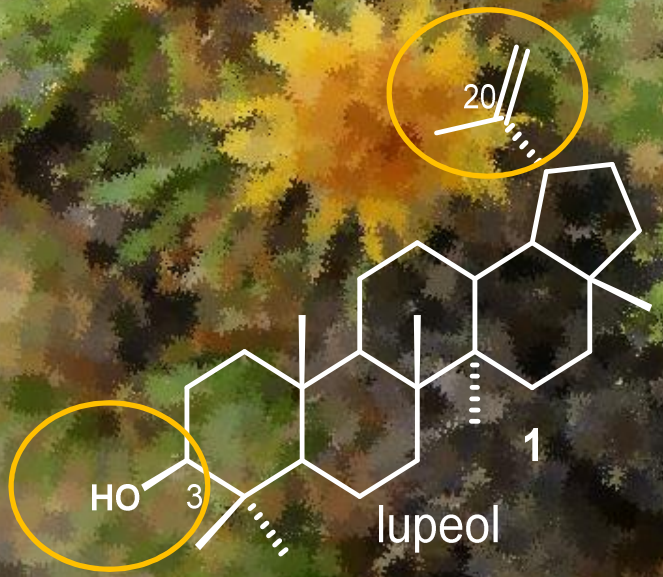
calenduladiol



lupeol

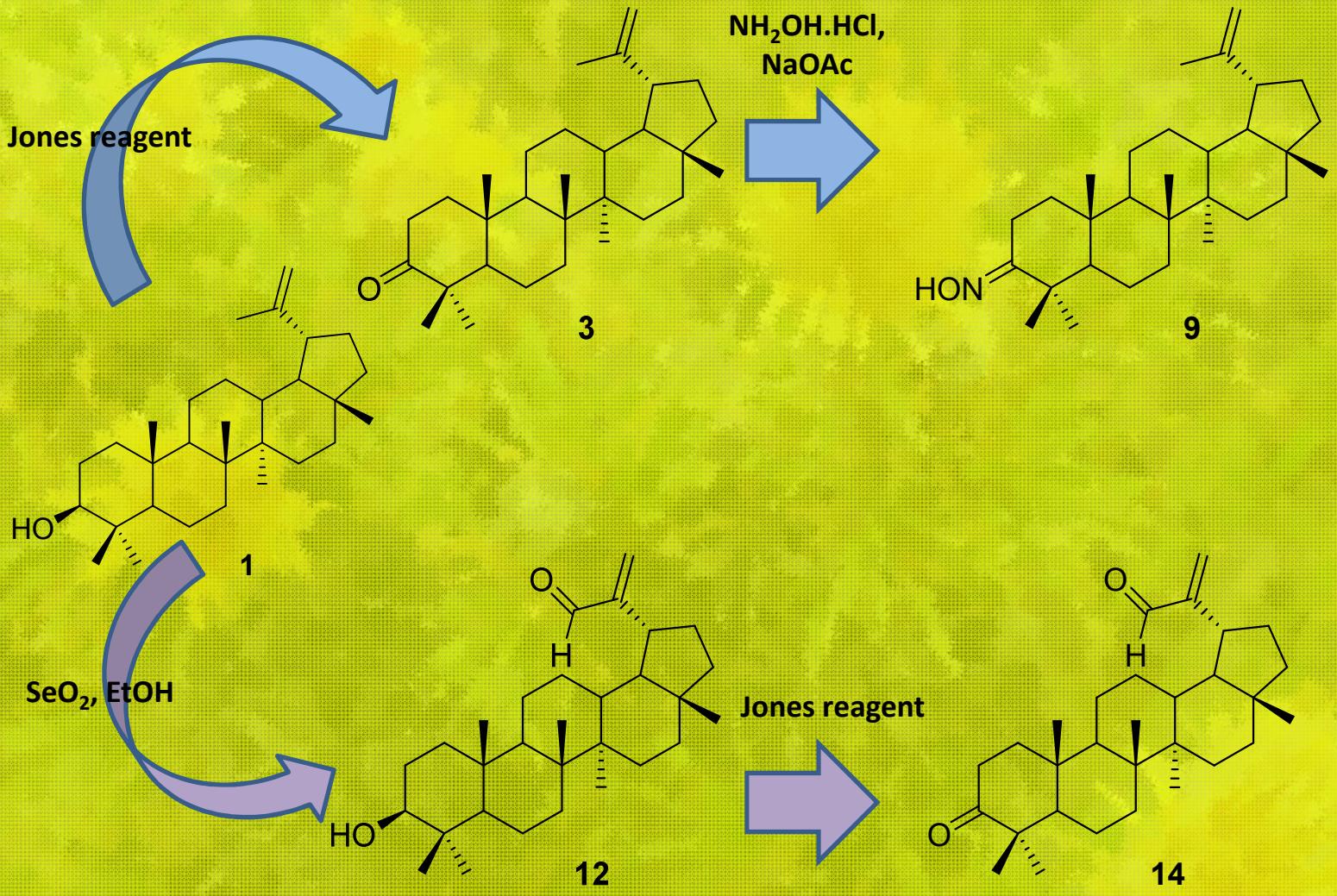
As a part of our continuing efforts directed toward the synthesis of new cholinesterase inhibitors, we became interested in evaluate the role of the keto group at C-16.



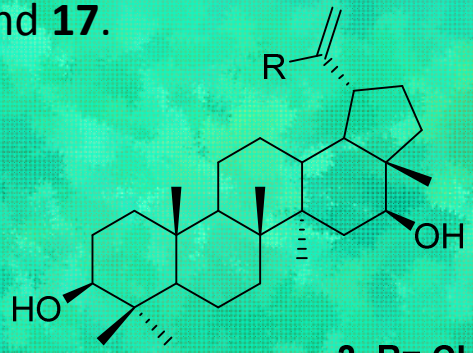


In order to confirm the importance of the keto group at C-16 on the antiBChE activity, we compared the same derivatives of calenduladiol (2) unfunctionalized at C-16 obtained from lupeol (1)

Semisynthetic lupanes **3**, **9**, **12** and **14** have been prepared from lupeol (**1**) by oxidation or sequential oxidations and by reaction with hydroxylamine hydrochloride.

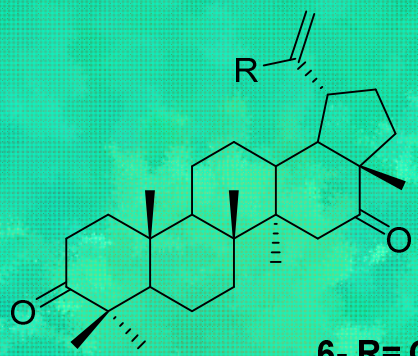


Ketones **4 -6** and **15** were obtained by Jone´s oxidation of compounds **2** and **13**. Further reaction of **6** and **15** with hydroxylamine hydrochloride provided compounds **10**, **11**, **16** and **17**.



2- R= CH_3
13- R= CHO

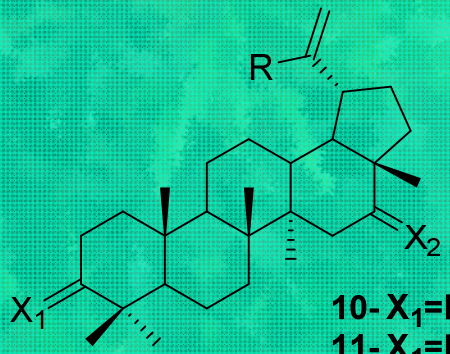
a)



+ 4 + 5

6- R= CH_3
15- R= CHO

b)



10- X_1=NOH X_2=O R= CH_3
11- X_1=NOH X_2=NOH R= CH_3
16- X_1=NOH X_2=O R= CHNOH
17- X_1=NOH X_2= NOH R= CHNOH

(a) Jones reagent; (b) $NH_2OH.HCl$, NaOAc, $EtOH/H_2O$.

Compounds **7** and **8** were obtained by SeO_2 oxidation of compounds **4** and **5** respectively.

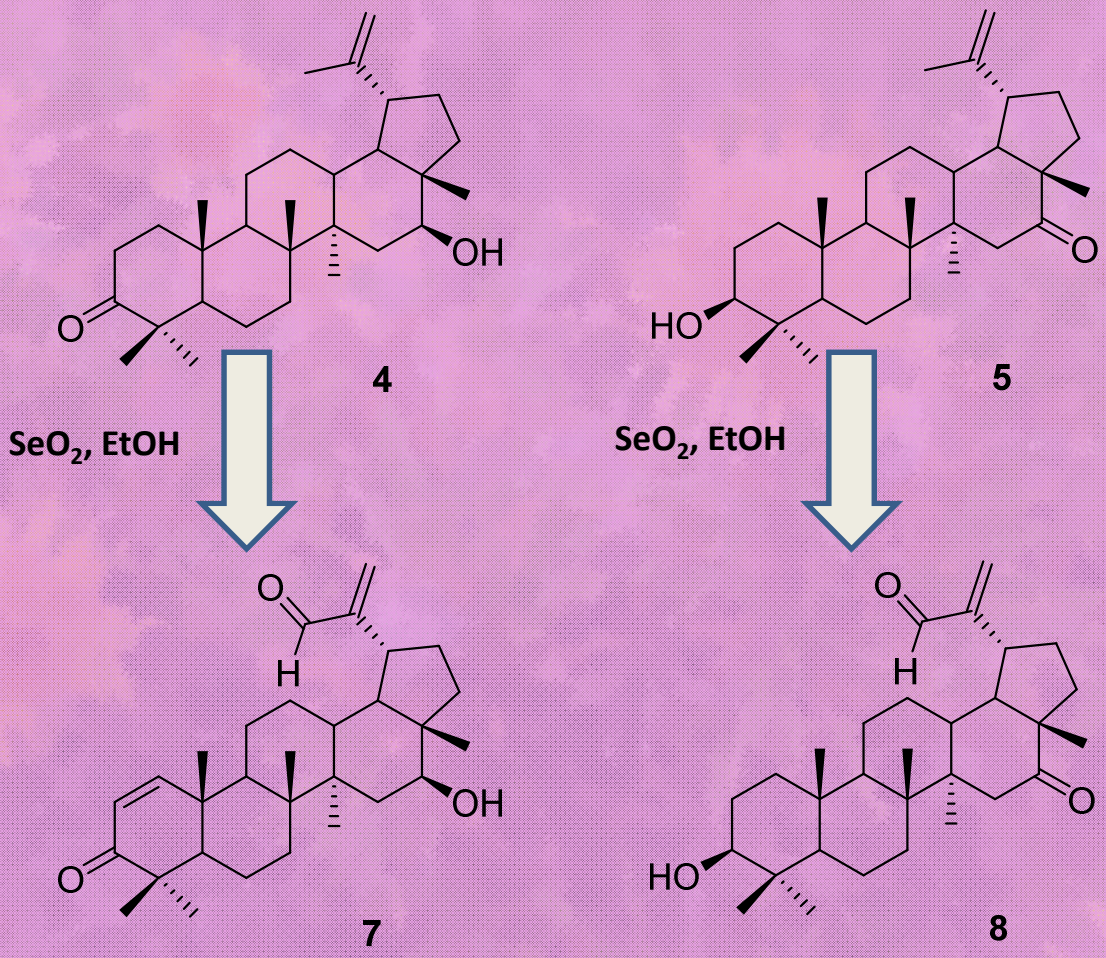
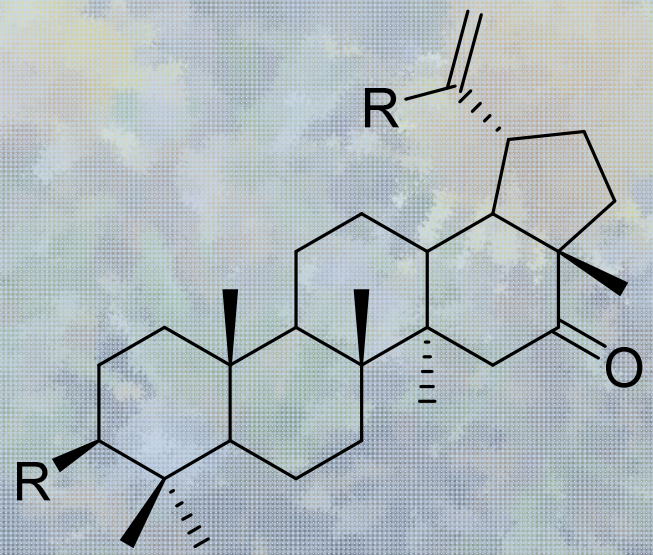


Table 1. Inhibition of AChE and BChE activity and selectivity index.

	AChE [a]		BChE [b]		
Compounds	% inhibition at 200 µM	IC_{50} (µM)	% inhibition at 200 µM	IC_{50} (µM)	Selectivity index [c]
1	21.3 ± 2.7	> 200	31.0 ± 2.2	> 200	
2	8.1 ± 0.2	> 200	42.0 ± 0.8	> 200	
3	5.7 ± 0.4	-	3.2 ± 1.0	-	
4	12.6 ± 1.5	> 200	43.5 ± 0.9	> 200	
5	40.2 ± 2.1	> 200	> 100	28.9 ± 0.1	> 6.92
6	6.4 ± 0.3	-	61.4 ± 0.5	154.6 ± 2.3	
7	n.i.[d]	-	44.6 ± 0.6	> 200	
8	29.7 ± 0.8	> 200	> 100	76.8 ± 0.3	> 2.60
9	5.3 ± 1.0	-	43.7 ± 0.4	> 200	
10	7.6 ± 1.2	-	82.8 ± 0.9	83.7 ± 0.1	
11	2.4 ± 1.0	-	47.4 ± 0.7	> 200	
12	8.8 ± 1.2	-	10.2 ± 1.4	-	
13	43.5 ± 1.1	> 200	42.0 ± 4.4	-	
14	n.i.[d]	-	28.9 ± 3.1	-	
15	21.7 ± 1.2	> 200	86.5 ± 2.7	21.5 ± 1.2	> 9.30
16	n.i.[d]	-	55.1 ± 1.2	174.2 ± 0.1	
17	4.3 ± 1.5	-	29.2 ± 1.0	-	
eserine	-	0.011 ± 0.001	-	0.014 ± 0.001	
tacrine	-	0.029 ± 0.002	-	0.004 ± 0.001	

Conclusions

Our results on BChE inhibition of calenduladiol analogs which have been oxidized at the C-16 position indicate that they could be promising leader compounds to develop a strategy for the enhancement of pharmacological properties of this type of BChE inhibitors.



Acknowledgements

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