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ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · NOVEMBER 2009

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2009.10.039 · Source: PubMed

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Original article

Synthesis and AChE inhibitory activity of new chiral tetrahydroacridine analogues from terpenic cyclanones

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ARTICLE INFO

Article history:
Received 4 June 2009
Received in revised form
14 October 2009
Accepted 27 October 2009
Available online 10 November 2009

Keywords:
Acridines
Tacrine
AChE inhibitory activity

ABSTRACT

This work describes the enantioselective synthesis of a new series of terpenic chiral 9-amino-tetrahydroacridine analogues. Several chiral ketones were synthesized from natural monoterpenes in an optically active form and subjected to the cyclodehydration reactions with anthranilonitrile in the presence of $BF_3 \cdot Et_2O$ as catalyst. The 9-aminotetrahydroacridine analogues were tested as acetylcholinesterase (AChE) inhibitors. Based on qualitative structure–activity relationship some trends are suggested.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that results in the progressive and irreversible loss of higher brain functions, including memory, cognition and reason [1–4]. Current treatment approaches for this disease remain primarily symptomatic, with the major therapeutic strategy being based on the cholinergic hypothesis [1,5–7] and specifically on acetylcholinesterase inhibition [8–10]. Under this hypothesis, the first approved drug for the management of AD was tacrine (**1a**, 9-amino-1,2,3,4-tetrahydroacridine or THA, Fig. 1), a potent inhibitor of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). However, the use of tacrine in AD has been limited by serious side effects such as hepatotoxicity, which often forces patients to discontinue treatment [11–14]. Tacrine has also been shown to possess a much broader pharmacological profile than cholinesterase inhibition: blockage of potassium channels [15,16], inhibition of the neuronal monoamine uptake processes [17,18], and inhibition of monoamine oxidase [19], have all been reported.

An important contribution to the development of tacrine related agents showed that tacrin-1-ol (**1b**, velnacrine) [20], an active metabolite of tacrine, has been chosen for clinical trial. 6-Fluorotacrin-1-ol (**1c**) has been reported to be slightly more potent than tacrine, and 6-chlorotacrin-1-ol (**1d**) 30 times more potent [21]. In particular 6-chlorotacrine (**1e**) has been found to be more potent than other substituted analogues [22,23].

(−)-Huperzine A (HA, **2**), an alkaloid first isolated from *Huperzia serrata* [24], is another AChE inhibitor. (−)-HA (**2**) is currently in the phase IV clinical trial for AD treatment in China and in clinical trials for the treatment of age-related memory deficiency in the United States [25,26].

Despite achievements in synthesis and pharmacomodulation, huprines **3**, a series of tacrine-huperzine A hybrids designed by the combination of the 4-aminoquinoline moiety of tacrine with the carbobicyclic substructure of (−)-HA (**2**), have recently emerged as a new class of very potent and selective AChE inhibitors of interest for the treatment of AD [27]. At present, the most powerful huprines are the so-called huprine **X** (**3a**) and huprine **Y** (**3b**) [28]. Indeed, huprines can be regarded as tacrine analogues modified at the cyclohexene ring, namely at positions C1 and C3 of the tacrine system, also in enantiopure forms [29–32].

In this regard, few reports exist in the literature dealing with enantioselective modification of tacrine structure in the saturated C-Ring (C_1–C_4 positions) [33,34]. In 1997 McKenna and co-workers, in their reported results on the synthesis of novel THA analogues, described the first example of a chiral THA analogue, which was

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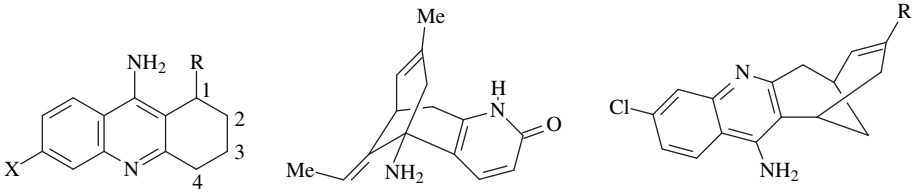
doi:10.1016/j.ejmech.2009.10.039



1a, X = R = H
1b, X = H, R = OH
1c, X = F, R = OH
1d, X = Cl, R = OH
1e, X = Cl, R = H

2 (-)-huperzine A

3a (-)-huprine X R = Et
3b (-)-huprine Y R = Me

Fig. 1. AChE inhibitors of interest for the treatment of Alzheimer's disease.

obtained by the condensation reaction of anthranilonitrile and (*R*)-(+)-camphor in the presence of $BF_3 \cdot Et_2O$ as catalyst, in 18% yield [16]. Recently, Frideling and co-workers described the synthesis of a series of chiral tetrahydroacridin-9-ones, derived from chiral cyclanones such as (*R*)-(+)-3-methylcyclohexanone, (*2S,5R*)-(−)-menthone, (*R*)-(+)-pulegone, (*R*)-(−)-carvone and (*5R*)-(+)-dihydrocarvone by the reaction of anthranilic acid under classical heating or under microwave irradiation [33]. Also in this work, Frideling and co-workers described the synthesis of 9-aminotetrahydroacridines derived from the cyclodehydratation reaction between cyclohexanones (menthone, 3-methylcyclohexanone) and anthranilonitrile using microwave irradiation, but in this case yields were between 12% and 18%, even using solid supports (silica, basic alumina, montmorillonite K10 and KSF).

Terpenes as chirons have an intrinsic advantage over other natural products in the 'chiral pool', as they are amenable to restructuring into cyclic and acyclic fragments that can be directly incorporated into the carbocyclic framework of complex target structures.

As part of our studies directed towards the enantioselective synthesis of building blocks from terpenes [35,36], we describe herein the enantioselective synthesis of a new series of chiral tetrahydroacridine analogues **7** (Scheme 1).

The construction of terpenic chiral THA analogues from synthetic ketones relies on availability for specific reactions to elaborate and couple them.

For this purpose, several chiral ketones **5** were synthesized from natural monoterpenes in an optically active form and subjected to the cyclodehydration reactions with anthranilonitrile (**4**) in the presence of $BF_3 \cdot Et_2O$ as catalyst. The new series of chiral tetrahydroacridine analogues thus obtained were assayed for their ability to inhibit AChE.

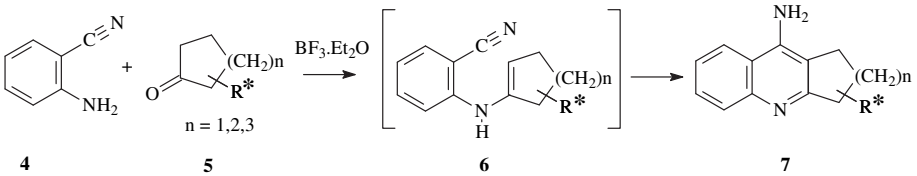
2. Results and discussion

2.1. Chemistry

Regarding the synthesis of the terpenic chiral ketones used in this work (Table 1), the (*S*)-(−)-3-isopropenylcyclohexanone (**12**) was prepared from (*S*)-perillaldehyde (**30**) in approximately 45% yield by a synthetic route previously reported by our group (Scheme 2) [35]. The key strategic feature is the thiophenoxide opening of the α,β-epoxy ketones **31** with concomitant retro-aldol expulsion of acetone and subsequent desulfenylation of **32** by thiophenoxide to afford (*S*)-**12**. Hydrogenation of the isopropenyl double bond in (*S*)-**12** using PtO_2 as the catalyst in methanol at 1 atm of hydrogen furnished the (*S*)-(−)-3-isopropylcyclohexanone (**8**) in 94% yield, which was used directly in the cyclocondensation reaction.

As an extension of this synthetic route, the α,β-epoxy ketones **31** were subjected to deoxygenation with the use of an equimolar amount of $Mo(CO)_6$ under toluene reflux to afford a mixture of enone **33** and the expanded 1,3-diketone **34**, which were separated by column chromatography in a ratio of 5 : 1 (Scheme 3). The selective hydrogenation of **33** in the presence of $Rh(PPh)_3Cl$ afforded **20** in high yield (94% after purification by column chromatography). Hydrogenation of **34** using PtO_2 as the catalyst led to **19** in 85% yield. The reduction of the enone **33** using sodium tellurium hydride led to a mixture of ketones **35a** and **35b** in 87% yield, in a ratio of 2:1, which were separated by column chromatography (Scheme 4). Hydrogenation of the isopropenyl double bond in **35a** using PtO_2 as the catalyst afforded *trans*-diisopropylcyclohexanone (**24**). In the case of *cis*-isomer **35b**, isomerization of the isopropyl group in α-position to the carbonyl group was observed, when subjected to hydrogenation under a variety of conditions in the presence of several catalysts.

The acid-catalyzed retro-aldol reaction of (*R*)-pulegone (**36**) (HCl_{aq}, reflux, 8 h), using standard conditions [37] led in 70% yield to (*R*)-3-methylcyclohexanone (**10**), obtained without loss of optical activity. (*R*)-3-methylcyclopentanone (**15**) was also prepared from (*R*)-pulegone (**36**) in 66% yield in two reaction steps. Oxidative cleavage of (*R*)-pulegone using $RuCl_3/NaIO_4$ afforded the (*R*)-3-methyladipic acid **37** [38]. Next, **37** was subjected to ketonic decarboxylation and cyclization processes in the presence of catalytic Na_2CO_3 under thermal conditions (Scheme 5) [39]. Mechanistic considerations, for the later reaction, involve an initial ketonic decarboxylation, followed by the attack of an unstable carbanion to the second carboxyl group, leading to the cyclopentanone **15**. (*R*)-2,2,5-trimethylcycloheptane-1,3-dione (**17**) was obtained in high yield (90%) by a $BF_3 \cdot Et_2O$-catalyzed



4 **5** **6** **7**

Scheme 1. Cyclocondensation reaction between anthranilonitrile and chiral cyclanones.

Table 1
9-Aminotetrahydroacridines synthesized from chiral terpenic cyclanones.

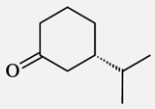
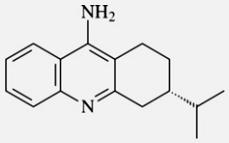
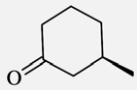
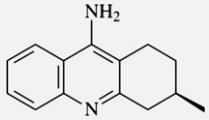
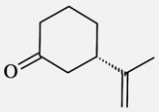
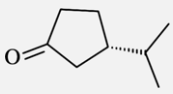
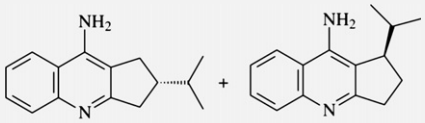
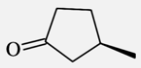
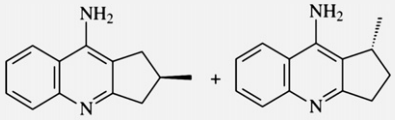
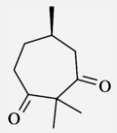
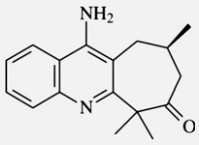
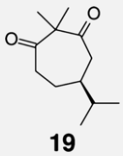
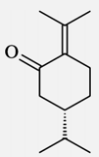
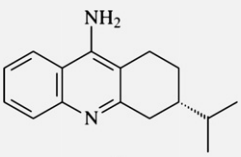
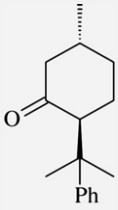
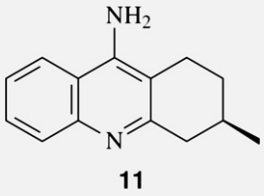
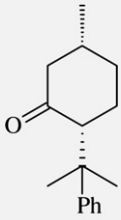
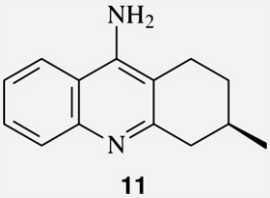
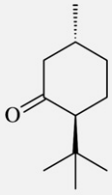
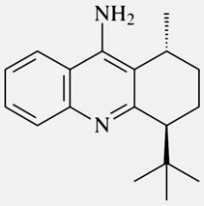
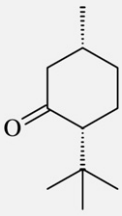
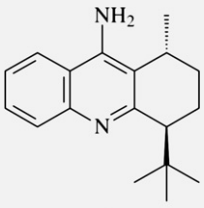
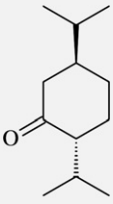
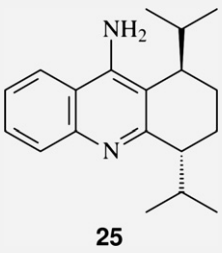
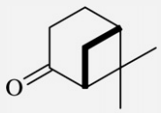
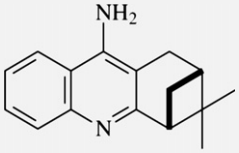
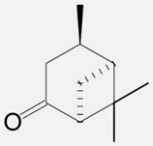
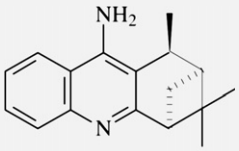
Entry	Substrate	Product	$[\alpha]_D$ (conc.)[a]	Yield (%)[b]
1	 **8**	 **9**	−52 (1.64)	84
2	 **10**	 **11**	+38 (1.50)	82
3	 **12**	Complex Mixture		
4	 **13**	 **14a** (3.5) : **14b** (1)	−18 (0.29) for **14a**	68
5	 **15**	 **16a** (3) : **16b** (1)	−2 (1.10) for **16a**	75
6	 **17**	 **18**	+17(1.5)	78
7	 **19**	No Reaction		
8	 **20**	 **9**	−52 (1.64)	57

Table 1 (*continued*)

Entry	Substrate	Product	$[\alpha]_D$ (conc.)[a]	Yield (%)[b]
9	 **21a**	 **11**	+38 (1.50)	65
10	 **21b**	 **11**	+38 (1.50)	52
11	 **22a**	 **23**	−111 (0.45)	58
12	 **22b**	 **23**	−111 (0.45)	35
13	 **24**	 **25**	−45 (0.72)	48

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product	$[\alpha]_D$ (conc.)[a]	Yield (%)[b]
14	 **26**	 **27**	−32 (1.70)	57
15	 **28**	 **29**	+15 (1.42)	63

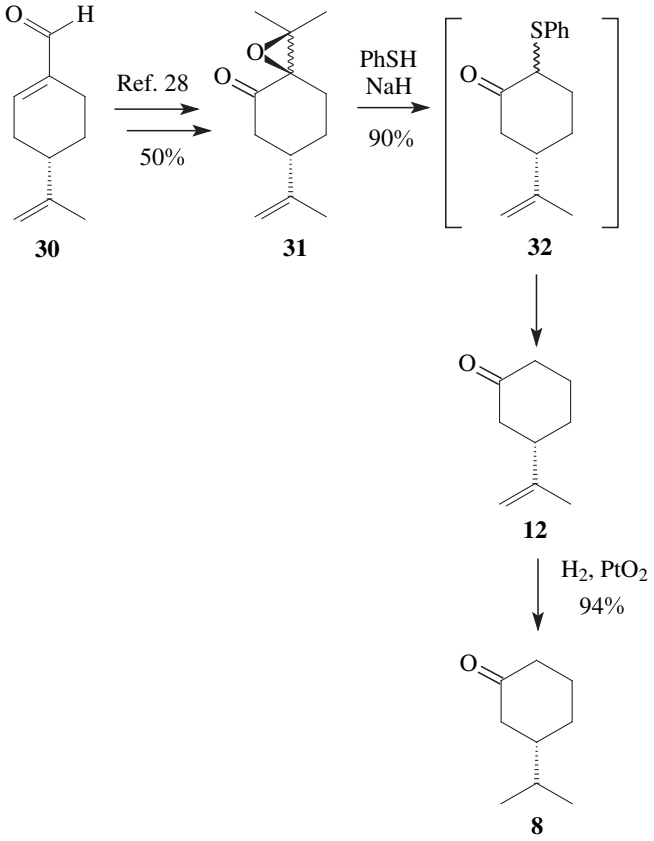
[a] Optical rotations were measured in $CHCl_3$ at 20 °C.
[b] All yields refer to purified product.

rearrangement from pulegone oxide [40]. Also, the *cis* and *trans* stereomers of methyl and phenyl (*R*)-pulegone derivatives **22a**, **22b**, **21a** and **22b** were easily prepared by conjugated addition of Me_2CuLi and PhMgBr/CuI respectively, as previously described in the literature [41,42].

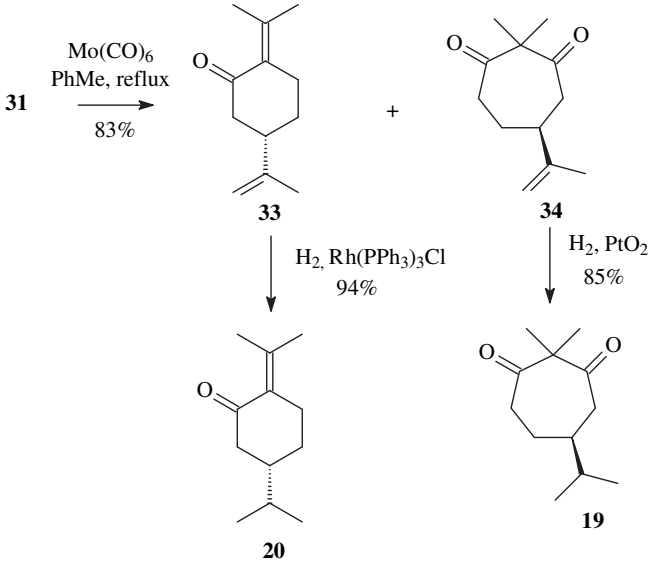
(*S*)-3-isopropylcyclopentanone (**13**) was prepared as depicted in Scheme 6. The synthetic route includes the initial conversion of (*S*)-perillaldehyde (**30**) in allylic alcohol **38**. Subsequent epoxidation of **38** to **39** followed by oxidative cleavage afforded (*S*)-3-isopropylhexanedioic acid (**40**) [43,44]. In the next step, diacid **40** was heated at 350 °C in the presence of a catalytic amount of Na_2CO_3 to give **13** in 35% general yield from (*S*)-perillaldehyde (**30**).

(+)-Nopinone (**26**) was prepared from β-pinene using $RuCl_3$ (0.023 equiv) and $NaIO_4$ (2.1 equiv) in 81% yield [45,46]. It is noteworthy that this method offers advantages over the traditional ozonolysis used to effect this operation, which is known to be quite hazardous due to occurrence of explosions. The optically active *cis*-verbanone (**28**) was prepared from the (*S*)-verbenone in high selectivity and good yield (78%), employing catalytic transfer hydrogenation in the presence of limonene and 10% Pd/C, according to the method described by Holleben et al. [47].

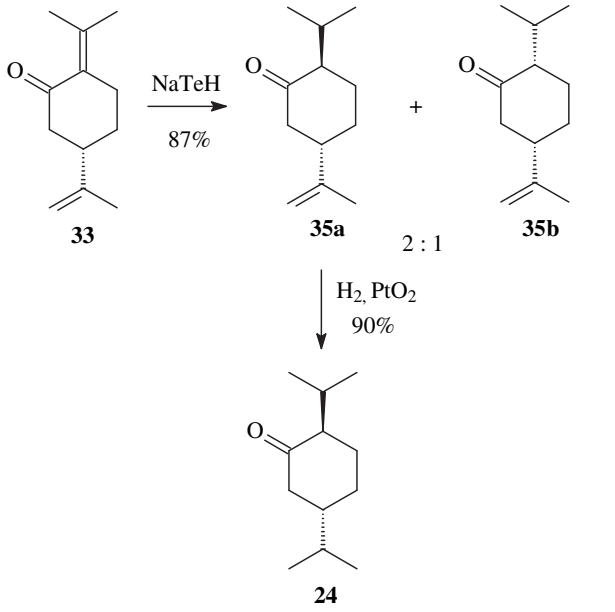
The cyclodehydratation reactions between the ketones and anthranilonitrile were performed according to the standard methodology for the synthesis of tacrines, by the Lewis acid promoted Friedländer reaction. It is noteworthy from a mechanistic viewpoint that an intermediate, probably enamine **6**, was first formed, which then converted to tetrahydroacridine (Scheme 1). Among several catalysts reported in the literature, such as $ZnCl_2$ [48], $AlCl_3$ [49], P_2O_5 [50], and $BF_3{\cdot}Et_2O$ [16], the catalyst of choice for this work was $BF_3{\cdot}Et_2O$. As described in the literature, also in



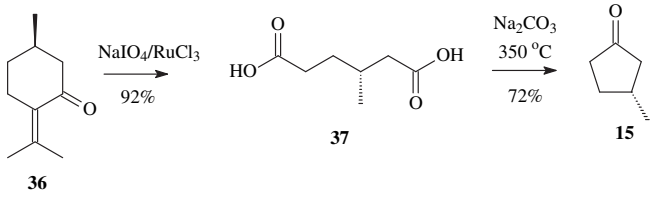
Scheme 2. Synthetic pathway for the preparation of compound **8**.



Scheme 3. Synthetic pathway for the preparation of compounds **19** and **20**.



Scheme 4. Synthetic pathway for the preparation of compound **24**.



Scheme 5. Synthetic pathway for the preparation of compound **15**.

our hands, $BF_3 \cdot Et_2O$ proved to be an effective catalyst for the cyclodehydratation reactions, giving the best overall yield and highest purity, using cyclohexanone and anthranilonitrile as the model substrate [16,34]. Next, we examined the reactivity and product selectivity of the cyclocondensation reaction with several chiral terpenic cyclanones synthesized for this purpose, as depicted in Table 1.

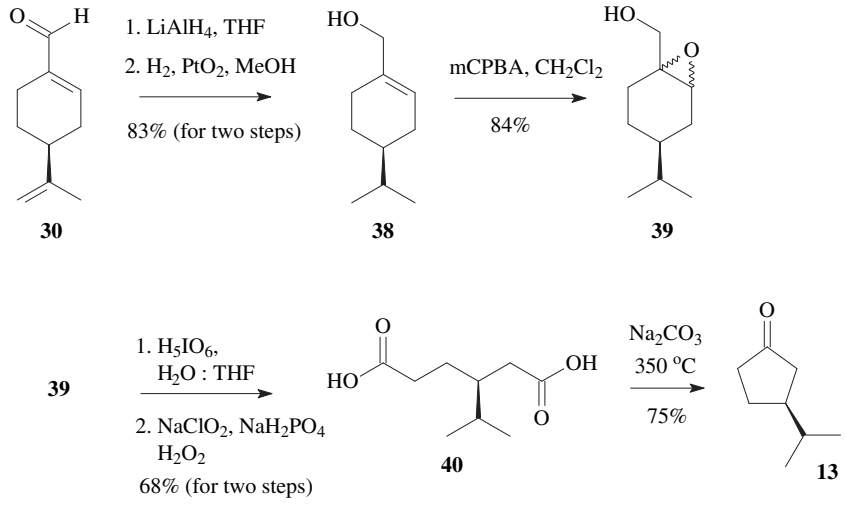
The cyclocondensation reaction using (*S*)-(−)-3-isopropylcyclohexanone (**8**) and (*R*)-(+)-3-methylcyclohexanone (**10**) occurred in a completely regioselective manner giving, respectively, optically active **9** and **11** in good yields (entries 1 and 2). Not all the substrates tested proved as susceptible to the cyclocondensation reaction. In the case of (*S*)-(−)-3-isopropenylcyclohexanone (**12**) (entry 3), the acidic reaction conditions brought about isomerization to a substantial extent and a complex mixture was observed by NMR analysis.

As can be seen from entries 4 and 5, both cyclopentanones **13** and **15** afforded a mixture of the corresponding isomers (**14a**, **14b** in a ratio of 3.5:1 and **16a**, **16b** in a ratio of 3:1), which proved to be difficult to separate by column chromatography. In both cases, a small amount of the major isomers **14a** and **16a** could be isolated. (*R*)-2,2,5-trimethylcycloheptane-1,3-dione (**17**, entry 6) and (*S*)-5-isopropyl-2,2 dimethylcycloheptane-1,3-dione (**19**, entry 7) were subjected to the cyclocondensation reaction. In the case of **17** as substrate, the reaction led to the chemoselective formation of the tacrine analogue **18** in 78% yield. However, isopropyl-substituted 1,3-dione **19** was not reactive under similar reaction conditions and starting material was recovered unchanged. Next, we performed the reaction with enone **20** (entry 8). Under the reaction conditions employed, the cyclocondensation reaction led only to **9** (identical to that obtained from (*S*)-(−)-3-isopropylcyclohexanone). The cleavage of the methylethylidene group observed has precedence in the reaction of cyclocondensation between pulegone and anthranilic acid, under thermal or microwave irradiation conditions, to afford the corresponding 3-methyltetrahydroacridinone [33].

Fragmentation was also observed in the case of both stereomers **21a** and **21b** (entries 9 and 10), with the elimination of the methyl-1-phenylethyl group, yielding the product **11**. Using (2*S*,5*R*)-2-*tert*-butyl-5-methylcyclohexanone (**22a,** *trans* isomer), the formation of the *trans* isomer **23** was observed. Also, **23** was observed as the product performing the reaction with the *cis*-isomer **22b**, which underwent isomerization to the most stable form.

When the reaction was performed using (*2R*,*5S*)-2,5-diisopropylcyclohexanone (**24**) as starting material, the cyclocondensation reaction led to the corresponding product **25** and no fragmentation or isomerization products were observed in this case.

The bicyclic ketones (+)-nopinone (**26**) and *cis*-verbanone (**28**) afforded the respective tetracyclic chiral tacrine analogues **27** and **29** (entries 14 and 15). It is noteworthy that no side product from



Scheme 6. Synthetic pathway for the preparation of compound **13**.

Table 2
Structures and ChE inhibitory activities of tacrine analogues.

Compound	AChE inhibition (IC_{50}) (μM)[a]
Tacrine (**1a**)	0.088
9	0.816
11	1.384
14a	2.446
16a	0.061
18	0.288
23	1.352
25	7.217
27	1.931
29	2.616

[a] ±95% Confidence limits.

ring opening of the bicyclic ketones **26** and **28** was observed under the reaction conditions employed.

The new 9-aminotetrahydroacridines synthesized in this work were identified by the usual spectroscopic and analytical methods, and also by comparison with the ^1H and ^{13}C NMR assignment of the 9-aminotetrahydroacridines and tetrahydroacridin-9-ones previously synthesized by Frideling [33].

2.2. AChE inhibition evaluation

To determine the potential interest of the chiral terpenic THA analogues synthesized, AChE (rat cortex) inhibitory potency was measured by the principle of the Ellman method (Table 2) [51]. To allow comparison of the results, tacrine (**1a**) was used as the reference compound. Analogue **16a** was effective inhibitor of AChE and slightly more potent than prototype tacrine, and the most active in the assayed series. All the other analogues examined were of lower activity than **1a**, the least active being **25**.

Structure–activity relationship analysis regarding variations around the cyclohexene ring of tacrine and their five and seven-membered analogues still have limited information. Also, not all synthesized analogues reported in the literature have been subjected to AChE activity evaluation [33,34].

The potency against AChE has been presumed to result from the increased bulk and flexibility of the saturated ring [34]. Some qualitative structure–activity relationship emerges from the above results. The analogue **25** having a trans configuration of isopropyl groups at the C-1 and C-4 positions in the cyclohexene ring strongly decreases the inhibitory potency in comparison to tacrine, while, in the analogue **23** having a *trans* configuration of methyl and tert-butyl groups, the decrease of inhibitory potency is less drastic. This result can be a consequence of steric increase caused by isopropyl substituent at C-1 in **25**, while the sterically larger *tert*-butyl group at C-4 leads to a lower decrease of inhibitory potency. This is an evidence that the bulk of alkyl substituent at C-1 plays an important role in the inhibitory activity, rather than C-4. Further support of this evidence comes from the comparison of the inhibitory potency for tetracyclic chiral tacrine analogues **27** and **29**. The presence of the methyl group at C-1 in **29** leads to a significant decrease of inhibitory potency.

In the cases of five-membered analogues **16a** and **14a**, a similar loss of activity was observed by replacing the methyl group by the isopropyl group. In the cases of **11** and **9** an inverse effect, however less substantial, was observed by replacing the C-3 methyl group by isopropyl. The seven-membered analogue **18** was found to be a significantly potent inhibitor as compared with other compound screened. In this particular case the polar carbonyl group should account to the observed inhibitory potency. Although our results indicate an effect of these tacrine analogs on AChE activity, particularly compound **16a**. Further studies should include other molecular targets such as butyrylcholinesterase or biochemical pathways, such as glutamate neurotransmission or amyloid precursor protein processing, pointed out as involved in the symptomatology of Alzheimer's disease [52,53].

3. Conclusion

Several synthetic routes were used to access specific chiral ketones in an optically active form. These ketones were subjected to the cyclodehydration reactions with anthranilonitrile in the presence of $BF_3 \cdot Et_2O$ as catalyst to afford the chiral 9-amino-tetrahydroacridine analogues in good yields. The products were obtained in high selectivity except in the cases of substituted five-membered ketones **13** and **15**. Compound **16a** was an effective inhibitor of AChE and slightly more potent than prototype tacrine. It is noteworthy that the decrease of inhibitory activity is a consequence of the increasing bulk of alkyl group at C-1 position.

4. Experimental protocols

Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. IR spectra were measured on a Mattson Galaxy Series FT-IR 3000 (model 3020). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. The chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and J standard values are given in Hz. Optical rotations were measured in a Perkin–Elmer 341 polarimeter with a 0.1 dm cell at a temperature of 20 °C. ESI-HRMS data on the positive mode were collected on a Waters® Micromass® Q-Tof micro mass spectrometer YB320 with Z-spray electrospray source. Samples were infused from a 100 μL gas-tight syringe at 30 μL/min. The instrument settings were the following: capillary voltage 3000 V, cone voltage 40 V, source temperature 100 °C, desolvation gas temperature 100 °C. Nitrogen was used as the desolvation gas. The samples were dissolved in an acetonitrile/milliQ water 1:1 solution (TEDIA) HPLC grade, made lightly acid with five drops of formic acid 0.1% solution. Purification by column chromatography was carried out on silica gel 60 (70–230 mesh). Analytical thin-layer chromatography (TLC) was conducted on Merck aluminum plates with 0.2 mm of silica gel 60F-254.

4.1. Synthesis

4.1.1. General procedure for the preparation of tetrahydroacridines

To a solution of the ketone (1.1 equiv) in anhydrous toluene was added anthranilonitrile (1.0 equiv) followed by addition of $BF_3 \cdot Et_2O$ (1.2 equiv) under argon. The reaction mixture was heated under reflux during 24 h. On cooling, the toluene was decanted and, to liberate the product, the remaining solids were treated with NaOH 2 mol L^{-1} solution and heated at reflux for 24 h. After cooling, the reaction mixture was extracted with $CHCl_3$, the organic layers were combined and dried over Na_2SO_4, filtrated and the solvent was evaporated under reduced pressure to give the desired product. The resultant solid was purified by silica gel flash chromatography using $MeOH/CH_2Cl_2$ or alumina chromatography using hexane/AcOEt as eluent to give pure compounds.

*4.1.1.1. (3S)-9-amino-3-isopropyl-1,2,3,4-tetrahydroacridine (**9**).* Following the general procedure, ketone **8** (200 mg, 1.43 mmol), toluene (4 mL), anthranilonitrile (154 mg, 1.30 mmol) and $BF_3 \cdot Et_2O$ (0.20 mL, 1.57 mmol) afforded amine **9** (264 mg, 1.10 mmol, 84%): $[\alpha]_D = -52$ ($c = 1.64$, $CHCl_3$); m.p. 119–123 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3489, 3330, 3170, 2954, 1637, 1577, 1500, 1427, 1377, 754; ^1H NMR ($CDCl_3$) δ 7.90 (d, 1H, $J = 8.4$ Hz), 7.73 (d, 1H, $J = 8.4$ Hz), 7.55 (t, 1H, $J = 8.3$ Hz), 7.34 (t, 1H, $J = 8.3$ Hz), 4.83 (br s, 2H, NH_2), 3.10 (ddd, 1H, $J = 16.8$, 7.8,

2.1 Hz), 2.72 (dd, 1H, $J = 16.8, 10.8$ Hz), 2.70 (m, 1H), 2.52 (m, 1H), 2.08 (m, 1H), 1.61 (m, 2H), 1.49 (m, 1H), 0.99 (d, 6H, $J = 6.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 158.5, 146.6, 146.2, 128.5, 128.2, 123.8, 119.8, 116.9, 110.1, 40.2, 37.2, 32.0, 26.1, 23.8, 19.9, 19.4; MS (ESI+) calc. 240.1626, found 240.1618.

*4.1.1.2. (3R)-9-amino-3-methyl-1,2,3,4-tetrahydroacridine (**11**).* Following the general procedure, ketone **10** (200 mg, 1.78 mmol), toluene (5 mL), anthranilonitrile (191 mg, 1.62 mmol) and $BF_3 \cdot Et_2O$ (0.25 mL, 1.94 mmol) afforded amine **11** (282 mg, 1.33 mmol, 82%): $[\alpha]_D = +38$ ($c = 1.5$, $CHCl_3$); m.p. 196–198 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3484, 3293, 3055, 2919, 1643, 1565, 1498, 1437, 1376, 1279.

^{1}H NMR and ^{13}C NMR spectra gave the same absorptions as reported earlier [33].

*4.1.1.3. (2R)-9-amino-2-methyl-2,3-dihydro-1H-cyclopenta[b]quinoline (**16a**) and (1R)-9-amino-1-methyl-2,3-dihydro-1H-cyclopenta[b]quinoline (**16b**).* Following the general procedure, ketone **15** (200 mg, 2.04 mmol), toluene (6 mL), anthranilonitrile (219 mg, 1.85 mmol) and $BF_3 \cdot Et_2O$ (0.28 mL, 2.22 mmol) afforded amines **16a** (206 mg, 1.04 mmol, 56%) and **16b** (70 mg, 0.35 mmol, 19%).

*Data for **16a***: $[\alpha]_D = -2$ ($c = 1.1$, $CHCl_3$); m.p. 154–156 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3411, 3352, 3234, 2950, 1660, 1570, 1514, 1440, 1384; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, $J = 8.1$ Hz), 7.75 (d, 1H, $J = 8.1$ Hz), 7.56 (t, 1H, $J = 8.1$ Hz), 7.36 (t, 1H, $J = 8.1$ Hz), 4.82 (br s, 2H, NH_2), 3.24 (dd, 1H, $J = 16.0$, 7.5 Hz), 3.00 (dd, 1H, $J = 15.0$, 7.8 Hz), 2.74 (dd, 1H, $J = 16.0$, 7.2 Hz), 2.67 (m, 1H), 2.42 (dd, 1H, $J = 15.0$, 6.3 Hz), 1.20 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 147.7, 145.1, 128.8, 128.2, 123.7, 119.9, 117.7, 114.7, 43.3, 35.5, 31.9, 21.2; MS (ESI+) calc. 198.1157, found 198.1158.

*Data for **16b***: ^{13}C NMR ($CDCl_3$) δ 166.8, 148.8, 144.4, 128.3, 128.2, 123.7, 119.9, 119.7, 114.7, 34.8, 33.1, 31.5, 18.4.

*4.1.1.4. (2S)-9-Amino-2-isopropyl-2,3-dihydro-1H-cyclopenta[b]quinoline (**14a**) and (1R)-9-amino-1-isopropyl-2,3-dihydro-1H-cyclopenta[b]quinoline (**14b**).* Following the general procedure, ketone **13** (200 mg, 1.59 mmol), toluene (5 mL), anthranilonitrile (170 mg, 1.44 mmol) and $BF_3 \cdot Et_2O$ (0.22 mL, 1.73 mmol) afforded amines **14a** (172 mg, 0.76 mmol, 53%) and **14b** (49 mg, 0.22 mmol, 15%):

*Data. for **14a***: $[\alpha]_D = -18$ ($c = 0.29$, $CHCl_3$); m.p. 167–169 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3444, 3359, 3243, 2956, 1650, 1569, 1438, 1384; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H, $J = 8.1$ Hz), 7.72 (d, 1H, $J = 8.1$ Hz), 7.57 (t, 1H, $J = 8.1$ Hz), 7.38 (t, 1H, $J = 8.1$ Hz), 4.67 (br s, 2H, NH_2), 3.18 (dd, 1H, $J = 16.6$, 8.4 Hz), 2.96 (dd, 1H, $J = 15.2$, 8.5 Hz), 2.84 (dd, 1H, $J = 16.7$, 9.6 Hz), 2.52 (dd, 1H, 15.1, 8.6 Hz), 2.28 (m, 1H), 1,73 (m, 1H), 1.03 (d, 3H, $J = 6.6$ Hz), 1.01 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 166.8, 148.1, 144.4, 128.7, 128.4, 123.9, 119.9, 117.7, 115.1, 45.1, 39.8, 33.6, 32.0, 21.1, 20.8; MS (ESI+) calc. 226.1470, found 226.1468.

*Data. for **14b***: (from crude product) ^{13}C NMR ($CDCl_3$) δ 167.6, 148.4, 145.0, 128.6, 128.2, 123.6, 120.1, 117.8, 117.5, 46.8, 34.4, 30.2, 23.9, 21.4, 17.5.

*4.1.1.5. (9R)-11-amino-6,6,9-trimethyl-9,10-dihydro-6H-cyclohepta[b]quinolin-7(8H)-one (**18**).* Following the general procedure, ketone **17** (200 mg, 1.19 mmol), toluene (3.5 mL), anthranilonitrile (128 mg, 1.08 mmol) and $BF_3 \cdot Et_2O$ (0.17 mL, 1.30 mmol) afforded amine **18** (226 mg, 0.84 mmol, 78%): $[\alpha]_D = +17$ ($c = 1.5$, $CHCl_3$); m.p. 121–123 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3463, 3388, 3254, 2963, 1699, 1641, 1579, 1498, 1426, 1374; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, 1H, $J = 8.4$ Hz), 7.74 (d, 1H, $J = 8.4$ Hz), 7.60 (t, 1H, $J = 8.3$ Hz), 7.42 (t, $J = 8.3$ Hz), 4.79 (br s, 2H, NH_2), 2.78–2.18 (m, 5H), 1.59 (s, 3H), 1.52 (s, 3H), 1.06 (d, 3H, $J = 4.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 215.4, 163.0, 146.7, 146.6, 129.8, 128.5, 124.8, 120.0, 117.8, 108.8, 56.3, 43.9, 32.8, 30.0, 24.5, 24.4, 20.4; MS (ESI+) calc. 268.1576, found 268.1570.

*4.1.1.6. (1S,4R)-9-amino-4-tert-butyl-1-methyl-1,2,3,4-tetrahydroacridine (**23**).* Following the general procedure, ketone **22a** (200 mg, 1.19 mmol), toluene (4 mL), anthranilonitrile (128 mg, 1.08 mmol) and $BF_3 \cdot Et_2O$ (0.17 mL, 1.30 mmol) afforded amine **23** (168 mg, 0.63 mmol, 58%): $[\alpha]_D = -111$ ($c = 0.45$, $CHCl_3$); m.p. 121–123 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3489, 3350, 3235, 2958, 1621, 1572, 1496, 1428, 1375; ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 1H, $J = 8.4$ Hz), 7.74 (d, 1H, $J = 8.4$ Hz), 7.56 (t, 1H, $J = 8.3$ Hz), 7.37 (t, 1H, $J = 8.3$ Hz), 4.80 (br s, 2H, NH_2), 3.07 (q, 1H, $J = 6.6$ Hz), 2.85 (dd, 1H, $J = 5.4$ Hz), 2.27 (tdd, 1H, $J = 13.8, 6.6, 3.3$), 2.11 (ddd, 1H, $J = 14.1, 6.3, 3.0$), 2.04 (ddd, 1H, $J = 14.2$, 5.4, 3.3), 1.58 (dt, 1H, $J = 13.5$, 3.3 Hz), 1.18 (d, 3H, $J = 6.9$ Hz), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.8, 145.7, 145.1, 129.0, 128.3, 123.9, 119.7, 117.5, 116.3, 48.7, 35.6, 30.4 (3Me, *t*Bu), 27.3, 26.7, 21.1, 19.9; MS (ESI+) calc. 268.1939 found 268.1938.

*4.1.1.7. (1R,4R)-9-amino-1,4-diisopropyl-1,2,3,4-tetrahydroacridine (**25**).* Following the general procedure, ketone **24** (200 mg, 1.10 mmol), toluene (3 mL), anthranilonitrile (118 mg, 1.00 mmol) and $BF_3 \cdot Et_2O$ (0.15 mL, 1.20 mmol) afforded amine **25** (137 mg, 0.48 mmol, 48%): $[\alpha]_D = -45$ ($c = 0.72$, $CHCl_3$); m.p. 137–139 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3488, 3349, 3146, 2956, 1622, 1572, 1495, 1382; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1H, $J = 8.4$ Hz), 7.73 (d, 1H, $J = 8.4$ Hz), 7.58 (t, 1H, $J = 8.3$ Hz), 7.39 (t, 1H, $J = 8.3$ Hz), 4.66 (s, 2H, NH_2), 3.09 (m, 1H), 2.90–2,70 (m, 2H), 2.21 (m, 1H), 2.02 (m, 1H), 1.89 (m, 2H), 1.56 (m, 1H), 1.10 (d, 3H, $J = 6.6$ Hz), 0.99 (d, 3H, $J = 6.6$ Hz), 0.79 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 161.8, 145.9, 145.6, 129.2, 128.1, 123.9, 119.8, 117.4, 115.5, 45.9, 39.2, 30.0, 29.8, 21.4, 21.1, 18.7, 17.2; MS (ESI+) calc. 282.2096, found 282.2089.

*4.1.1.8. (2R,4R)-9-amino-2,4-methano-3,3-dimethyl-1,2,3,4-tetrahydroacridine (**27**).* Following the general procedure, ketone **26** (200 mg, 1.45 mmol), toluene (4 mL), anthranilonitrile (156 mg, 1.32 mmol) and $BF_3 \cdot Et_2O$ (0.20 mL, 1.59 mmol) afforded amine **27** (179 mg, 0.75 mmol, 57%): $[\alpha]_D = -32$ ($c = 1.7$, $CHCl_3$); m.p. 131–133 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3363, 3240, 2959, 2933, 1638, 1567, 1502, 1433, 1376; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H, $J = 8.4$ Hz), 7.75 (d, 1H, $J = 8.4$ Hz), 7.57 (t, 1H, $J = 8.3$ Hz), 7.38 (t, 1H, $J = 8.3$ Hz), 4.69 (s br, 2H, NH_2), 3.10 (t, 1H, $J = 5.7$ Hz), 2.85 (m, 2H,), 2.77 (dd, 1H, $J = 7.2, 3.0$, Hz), 2.45 (m, 1H), 1.43 (s, 3H), 1.40 (d, 1H, $J = 9.9$ Hz), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.8, 146.1, 145.7, 128.7, 128.4, 124.1, 119.6, 118.5, 107.8, 50.4, 39.7, 39.5, 30.9, 27.7, 26.1, 21.2; MS (ESI+) calc. 238.1470, found 238.1475

*4.1.1.9. (1S,2S,4S)-9-Amino-2,4-methano-1,3,3-trimethyl-1,2,3,4-tetrahydroacridine (**29**).* Following the general procedure, ketone **28** (200 mg, 1.31 mmol), toluene (4 mL), anthranilonitrile (140 mg, 1.19 mmol) and $BF_3 \cdot Et_2O$ (0.18 mL, 1.43 mmol) afforded amine **29** (189 mg, 0.75 mmol, 63%): $[\alpha]_D = +15$ ($c = 1.42$, $CHCl_3$); m.p. 133–136 °C; IR (*KBr*) ν_{max}/cm^{-1}: 3378, 3254, 2959, 2933, 1644, 1554, 1502, 1453, 1388; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 1H, $J = 8.3$ Hz), 7,76 (d, 1H, $J = 8.3$ Hz), 7.56 (t, 1H, $J = 8.2$ Hz), 7.38 (t, 1H, $J = 8.2$ Hz), 4.72 (s br, 2H, NH_2), 3.19 (qd, 1H, $J = 7.2, 3.0$ Hz), 3.04 (t, 1H, $J = 5.4$ Hz), 2.71 (dt, 1H, $J = 9.9$, 5.8 Hz), 2.34 (td, 1H, $J = 6.0$, 3.0 Hz), 1.48 (d, 3H, $J = 7.2$ Hz), 1.45 (s, 3H), 1.34 (d, 1H, $J = 9.9$ Hz), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 146.2, 145.8, 128.6, 128.5, 124.1, 119.6, 119.1, 112.4, 51.8, 39.7, 48.3, 39.3, 35.1, 32.7, 27.1, 24.2, 17.4; MS (ESI+) calc. 252.1626, found 252.1629.

4.1.2. Preparation of chiral cyclanones

4.1.2.1. Synthesis of (S)-3-isopropylcyclopentanone (13)

4.1.2.1.1. (1RS,2RS,4S)-4-isopropyl-7-oxabicyclo[4.1.0]heptan-1-yl) methanol (39). To a stirred solution of allylic alcohol **38** (1.34 g, 8.7 mmol) in CH_2Cl_2 (60 mL) was added, slowly and at 0 °C, a solution of *m*CPBA 65% (2.24 g, 13.0 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred during 3 h while the temperature

was maintained at 0 °C. Next, sodium bisulfite 10% solution (100 mL) was added and the resulting mixture was stirred for 30 min at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with $NaHCO_3$ saturated solution (2 × 100 mL) and brine (2 × 100 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product **39** (1.37 g) was used without any further purification in the next step.

*Data for **39** (diastereomeric mixture)*: IR (*film*) ν_{max}/cm^{-1}: 3423, 2957, 2872, 1466, 1433, 1368, 1038, 1021, 842; ^1H NMR ($CDCl_3$) δ 3.72–3.51 (m, 2H), 3.32–3.22 (m, 1H), 2.12–1.70 (m, 4H), 1.69–1.02 (m, 5H), 0.86–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 64.5, 64.2, 60.6, 60.3, 57.1, 56.0, 39.4, 35.8, 32.1, 31.7, 28.5, 27.3, 26.1, 25.2, 24.6, 21.9, 19.6, 19.5, 19.3.

*4.1.2.1.2. (S)-3-isopropylhexanedioic acid (**40**).* To a stirred solution of epoxide **39** (1.3 g, 7.5 mmol) in 37 mL of THF-H_2O (10:1) at 0 °C was added H_5IO_6 (3.65 g, 16 mmol) in one portion. After 3 h, Et_2O (100 mL) and water (100 mL) were added. The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined organic layer was washed with brine (2 × 200 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford an aldehyde-acid (1.1 g), which was used without any further purification in the next step.

A solution of $NaClO_2$ (0.93 g, 8.13 mmol) in H_2O (8.1 mL) was added at 0 °C to a mixture of aldehyde-acid (1.0 g, 5.81 mmol) in MeCN (5.8 mL), NaH_2PO_4 (185 mg) in H_2O (2.3 mL) and 0.58 mL (0.61 mmol) of 35% H_2O_2 solution. After being stirred for further 2 h at same temperature, 60 mg of $Na_2S_2O_3$ were added and the mixture was acidified to pH 1 by the dropwise addition of 37% HCl and extracted with EtOAc (2 × 20 mL). The combined organic layers were extracted with saturated $NaHCO_3$ solution and brine. The aqueous extracts were combined, acidified to pH 1 by the dropwise addition of 37% HCl and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the diacid **40** (0.82 g) which was used without any further purification in the next step.

Data for aldehyde-acid: $[\alpha]_D = -6$ ($c = 1.30$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 2959, 2874, 1723, 1466, 1412, 1368, 1180, 1035; ^1H NMR ($CDCl_3$) δ 9.77 (t, 1H, $J = 1.8$ Hz), 2.50–2.25 (m, 1H), 2.35 (t, 2H, $J = 7.8$ Hz), 1.99–1.88 (m, 1H), 1.81–1.68 (m, 2H), 1.62–1.50 (m, 2H), 0.89 (d, 3H, $J = 6.9$ Hz), 0.86 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 202.9, 178.6, 45.1, 37.6, 31.9, 29.8, 26.4, 19.5, 18.2.

*Data for diacid **40***: $[\alpha]_D = -8$ ($c = 1.30$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 3044, 2962, 1708, 1413, 1371, 1285, 1219, 1163; ^1H NMR ($CDCl_3$) δ 10.10 (br, 1H), 2.42–2.34 (m, 1H,), 2.39 (t, 2H, $J = 7.5$ Hz), 2.18 (dd, 1H, $J = 16.5$, 7.5 Hz), 1.88–1.69 (m, 2H), 1.68–1.55 (m, 2H), 0.91 (d, 3H, $J = 6.6$ Hz), 0.87 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 180.2, 180.1, 40.0, 35.6, 32.1, 29.8, 26.1, 19.3, 18.3.

*4.1.2.1.3. (S)-3-isopropylcyclopentanone (**13**).* The crude mixture containing diacid 40 (0.82 g) and Na_2CO_3 (100 mg, 0.94 mmol) was heated at 350 °C during 30 min. The mixture was diluted with CH_2Cl_2 and filtered through celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluting with hexane–Et_2O, 8:2) to give (S)-3-isopropylcyclopentanone 13 in 35% of yield from (S)-perillaldehyde (**30**). $[\alpha]_D = -84$ ($c = 0.28$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 2962, 2874, 1746, 1406, 1386, 1160; ^1H NMR ($CDCl_3$) δ 2.52–2.27 (m, 2H), 2.25–2.07 (m, 2H), 1.94–1.76 (m, 2H), 1.62–1.54 (m, 2H), 0.96 (d, 3H, $J = 6.6$ Hz), 0.93 (d, 3H, $J = 6.6$ Hz) ^{13}C NMR ($CDCl_3$) δ 220.2, 44.6, 43.7, 39.1, 33.5, 27.7, 21.2, 20.3.

Specific rotation, IR data [54] ^1H and ^{13}C NMR data [54,55], were consistent with previously reported data for this compound.

*4.1.2.2. (S)-2-(isopropylidene)-5-(2-propenyl)-cyclohexanone (**33**) and (S)-2,2-dimethyl-5-(2-propenyl)-cycloheptane-1,3-dione (**34**).* To a stirred solution of epoxiketones **31** (505 mg, 2.56 mmol) in anhydrous toluene (6 mL) was added $Mo(CO)_6$ (676 mg, 2.56 mmol). The reaction mixture was heated at reflux for 4 h, allowed to cool, and filtered through celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluting with hexane-EtOAc, 99:1) to give enone **33** (332 mg, 1.86 mmol, 73%) and diketone **34** (52 mg, 0.27 mmol, 10%).

*Data for **33***: $[\alpha]_D = -28$ ($c = 1.3$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 3082, 2858, 1681, 1644, 1602, 1439, 1372, 1127, 1073; ^1H NMR ($CDCl_3$) δ 4.76 (s, 1H), 4.72 (s, 1H), 2.73 (dt, 1H, $J = 15.3$, 4.2 Hz), 2.55 (m, 1H), 2.45 (dt, 1H, $J = 11.4$, 3.6 Hz), 2.37–2.22 (m, 2H), 2.00 (s, 3H), 1.99–1.91 (m, 1H), 1.79 (s, 3H), 1.74 (s, 3H), 1.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 203.5, 147.5, 142.8, 131.4, 109.7, 47.3, 43.0, 29.3, 28.3, 23.0, 22.2, 20.5; MS (ESI+) calc. 178.1357, found 178.1363.

*Data for **34***: $[\alpha]_D = +79$ ($c = 1.4$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 3079, 2975, 2935, 2866, 1696, 1645, 1446, 1381, 1328, 1289, 1114, 1072, 987, 894; ^1H NMR ($CDCl_3$) δ 4.77 (s, 1H), 4.73 (s, 1H), 2.66–2.54 (m, 2H), 2.45 (dd, 1H, $J = 6.9$, 2.7 Hz), 2.44–2.36 (m, 2H), 2.09–1.98 (m, 1H), 1.84–1.65 (m, 1H), 1.72 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H,); ^{13}C NMR ($CDCl_3$) δ 212.2, 211.4, 147.6, 110.5, 61.4, 47.0, 45.7, 39.9, 33.1, 20.4, 20.3.

*4.1.2.3. (2R,5S)-2-isopropyl-5-(2-propenyl)-cyclohexanone (**35a**) and (2S,5S)-2-isopropyl-5-(2-propenyl)-cyclohexanone (**35b**).* A suspension of Te (861 mg, 6.73 mmol) and $NaBH_4$ (618 mg, 16.27 mmol) in anhydrous ethanol (18 mL) was heated at reflux for 2 h. The solution was allowed to cool at room temperature and a solution of the enone (300 mg, 1.68 mmol) in anhydrous ethanol (5 mL) was added. The resulting mixture was heated at reflux for 24 h under argon. Next, the reaction mixture was allowed to cool at room temperature and filtered through celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluting with hexane-EtOAc, 99:1) to give ketone **35a** (176 mg, 0.98 mmol, 58%) and ketone **35b** (88 mg, 0.49 mmol, 29%).

*Data for **35a***: $[\alpha]_D = +16$ ($c = 1.33$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 2956, 2937, 1709, 1645, 1179, 1082, 891; ^1H NMR ($CDCl_3$) δ 4.75 (s, 1H), 4.73 (s, 1H), 2.48–2.24 (m, 3H), 2.20–2.05 (m, 3H), 2.04–1.93 (m, 1H), 1.74 (s, 3H), 1.69–1.53 (m, 1H), 1.40 (dq, 1H, $J = 13.8$, 3.3, 1.30), 0.93 (d, 3H, $J = 6.6$ Hz), 0.87 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 211.8, 147.5, 109.5, 56.0; 47.5, 46.9, 30.6, 27.7, 25.8, 21.1; 20.4; 18.6; MS (ESI+) calc. 180.1514, found 180.1506.

*Data for **35b***: $[\alpha]_D = -88$ ($c = 1.33$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 2958, 2869, 1708, 1644, 1369, 1246, 893; ^1H NMR ($CDCl_3$) δ 4.79 (s, 1H), 4.71 (s, 1H), 2.49–2.28 (m, 3H), 2.15–1.91 (m, 3H), 1.80–1.64 (m, 3H), 1.74 (s, 3H), 0.94 (d, 3H, $J = 6.6$ Hz), 0.85 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 214.2, 147.4, 110.3, 57.2, 45.7, 44.5, 26.9, 26.4, 25.8, 20.9, 20.7, 19.8.

*4.1.2.4. (2R,5S)-2,5-diisopropylcyclohexanone (**24**).* The ketone **35a** (134 mg, 0.74 mmol) was dissolved in MeOH (2 mL) and treated with catalytic PtO_2 (1.0 mg, 0.004 mmol). The mixture was stirred vigorously for 1 h under hydrogen atmosphere. The reaction mixture was filtered through a pad of silica gel. The filtrate was evaporated and the residue was purified by silica gel column chromatography (eluting with hexane-EtOAc, 99:1) to give **24** (122 mg, 0.67 mmol) in 90% of yield. $[\alpha]_D = +14$ (1.51, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 2958, 2872, 1711, 1467, 1387, 1369, 1238, 1196; ^1H NMR ($CDCl_3$) δ 2.36 (ddd, 1H, $J = 12.9$, 3.3, 2.1 Hz), 2.22–1.98 (m, 4H), 1.95–1.82 (m, 1H), 1.65–1.44 (m, 2H), 1.43–1.22 (m, 2H), 0.96–0.82 (m, 12H) ^{13}C NMR ($CDCl_3$) δ 213.0, 56.2, 46.5, 46.1, 32.6, 28.8, 27.9, 25.9, 21.2, 19.6, 19.3, 18.6.

*4.1.2.5. (S)-5-isopropyl-2,2-dimethylcycloheptane-1,3-dione (**19**).* The diketone **34** (148 mg, 0.76 mmol) was dissolved in MeOH (2 mL) and treated with catalytic PtO_2 (1.0 mg, 0.004 mmol). The mixture was stirred vigorously for 1 h under hydrogen atmosphere. The reaction mixture was filtered through a pad of silica gel. The filtrate was evaporated and the residue was purified by silica gel column chromatography (eluting with hexane-EtOAc, 99:1) to give diketone **19** (127 mg, 0.65 mmol, 85%). $[\alpha]_D = +85$ ($c = 1.4$, $CHCl_3$); IR (*film*) ν_{max}/cm^{-1}: 3075, 2940, 2870, 1694, 1640, 1439, 1376, 1291; ^1H NMR ($CDCl_3$) δ 2.56–2.26 (m, 4H), 1.98–1.86 (m, 1H), 1.78–1.58 (m, 3H), 1.23 (s, 6H), 0.89 (d, 3H, $J = 6.9$ Hz), 0.86 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 212.8, 212.6, 61.4, 46.0, 43.9, 39.9, 33.2, 20.5, 20.4, 19.2, 18.9.

4.2. Inhibitory activities toward AChE

4.2.1. In vitro assay of brain acetylcholinesterase

Adult Wistar male rats (2–3 months), were supplied by Departament of Biochemistry-UFRGS. Rats were decapitated, the brain was rapidly dissected on ice into cortex and then weighed and homogenized in ten volumes of cold 10 mM Tris–HCl buffer, pH 7.2. Homogenates were centrifugated at 1000 g for 15 min at 4 °C; supernatants used as acetylcholinesterase sources were divided into aliquots and stored at −20 °C.

Enzyme samples in 20 mM phosphate buffer, pH 7.4 were incubated 150 s with 0.8 mM acetylthiocholine iodide in the presence of 10 mM 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), for color development (all chemicals from Sigma). Production of the yellow anion of 5-thio-2-nitrobenzoic acid was measured with a SPECTRAmax 190, 96-well plate reader, at 405 nm. Protein concentrations were determined by Peterson's modification of the procedure of Lowry et al. [56], using bovine serum albumin as standard.

4.2.2. Statistical analysis

All results are calculated as mean ± SD.mean. The triplicate measurements were performed at typically a total of four concentrations for the enzyme study. The IC_{50} values were determined from a plot of activity value of log (inhibitor) vs. response, which was processed by a software of GraphPad Prism 5.0.

Acknowledgements

The authors wish to thank the following Brazilian agencies for financial support and fellowships: CNPq, FAPERGS, PROPESQ – UFRGS.

Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version at, doi:10.1016/j.ejmech.2009.10.039.

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