Available online at www.sciencedirect.com

European Journal of Medicinal Chemistry 39 (2004) 37–48

EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY

www.elsevier.com/locate/ejmech

Original article

Tetrahydroacridin-9-ones, 9-chlorotetrahydroacridines, 9-amino-tetrahydroacridines and 9-(pyrazol-1-yl)-tetrahydroacridines derived from chiral cyclanones

Aline Frideling [a], Robert Faure [a], Jean-Pierre Galy [a], Ahmed Kenz [b],
Ibon Alkorta [c], José Elguero [c,*]

[a] *Laboratoire de valorisation de la chimie fine, faculté de sciences et techniques de St. Jérôme, Université d'Aix-Marseille III, avenue Escadrille Normandie-Niémen, 13397 Marseille cédex 20, France*

[b] *Laboratoire de bioinorganique structurale, centre scientifique de Saint Jérôme, Université d'Aix-Marseille III, avenue Escadrille Normandie-Niémen, 13397 Marseille cédex 20, France*

[c] *Instituto de Química Médica (CSIC), Centro de Química Orgánica 'Manuel Lora-Tamayo', Juan de la Cierva 3, 28006 Madrid, Spain*

Received 18 June 2003; accepted 3 October 2003

Abstract

A series of tetrahydroacridines related to tacrine have been synthesized starting from 3-methylcyclohexananone, menthone, pulegone, carvone and dihydrocarvone (both racemic and chiral). In many cases, the yields and purity of the compounds have been improved by the use of a microwave oven. These compounds have been characterized by ^{1}H and ^{13}C NMR data. To establish their relative configuration, the structure of (*1R,4R*)-(+)-9-chloro-1-methyl-4-isopropyl-1,2,3,4-tetrahydroacridine (*cis*-**10b**), derived from (*2S,5R*)-(–)-menthone, has been determined by X-ray. The chemical shifts of *cis*-**10b** and *trans*-**10b** have been calculated at the GIAO/B3LYP/6-31G* level and compared successfully with the experimental data.

Keywords: Tacrine; Acridines; X-ray; NMR; GIAO; Configuration

1. Introduction

The importance of tacrine (THA, Cognex®) in the treatment of Alzheimer's disease has prompted us to synthesize a series of related compounds. Our aim was to provide pharmacologists with derivatives in which the cycloalkyl ring is substituted that could lack the side effects of tacrine and improve its profile. Chiral compounds could be used to explore the receptor topology.

The synthetic methodology is summarized in Fig. 1. We will discuss successively the tetrahydroacridinones (tetramethylenequinolones) (**I**), the 9-chlorotetrahydroacridines (**II**), the 9-aminotetrahydroacridines (**III**) (the compound represented is tacrine itself) and the 9-pyrazolyltetrahydroacridines (**IV**). The starting materials are cyclohexanones having a methylene α to the carbonyl group. The originality of our approach is the use of natural or semisynthetic cyclohexanones (we will use the **a** letter for the racemic compound and the **b** one for the pure enantiomer): (*R*)-(+)-3-methylcyclohexanone, (*2S,5R*)-(–)-menthone, (*R*)-(+)-pulegone, (*R*)-(–)-carvone and (*5R*)-(+)-dihydrocarvone.

Obviously, the most interesting compounds of Fig. 1 are tacrine **III** (R = H) and its analogs [1]. Tetrahydroacridinones **I** have been described as inhibitors of acid gastric secretion (R = 2-tertbutyl) [2]. The 9-chlorotetrahydroacridines **II** are only used as intermediates. Amongst the modifications of the tacrine structure none concerns alkyl substituents at positions 1-4 [1i]. On the other hand, the 7-*tert*-butyl- and 7-cyclohexyl derivatives of **III** have been described as memory enhancers in a patent [3]. Finally, structures related to **IV**, but derived of fully aromatic acridines, have been studied by Stevens (9-substituted by 1,2,3-triazoles and benzotriazoles) [4] and by Plater (benzotriazoles) [5]. Cristea [6] has described a 1-(acridin-9′-yl)-pyrazolin-5-one.

---

* Corresponding author.

E-mail address: iqmbe17@iqm.csic.es (J. Elguero).

doi:10.1016/j.ejmech.2003.10.003

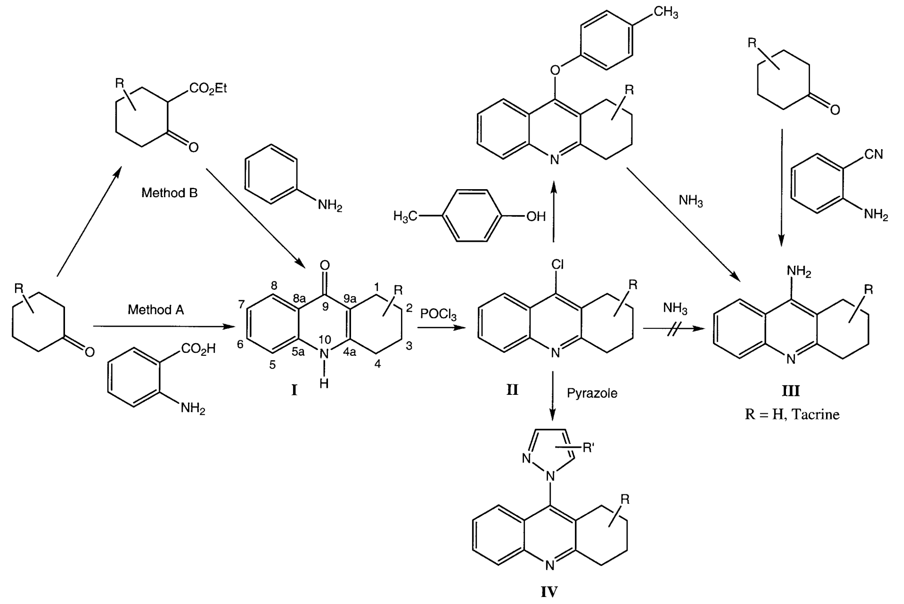


Fig. 1. Relationships between the different types of compounds prepared in this work.

2. Results and discussion

Before discussing the results gathered in Figs. 1, 2 and 3, it is useful to summarize the synthetic relationships (amines **12** and **13**, although formally related to chloro derivatives **8** and **9**, have not been prepared from them, the sign ⇒ represents only relationship not synthesis):

3-methylcyclohexanone → **1a** → **9a** ⇒ **12a**
(*R*)-(+)-3-methylcyclohexanone → **1b** → **9b** ⇒ **12b**
menthone → **2a** → **10a** ⇒ **13a**
(*2S,5R*)-(–)-menthone → **2b** → **10b** ⇒ **13b**
pulegone → **3a** → **11a**
(*R*)-(+)-pulegone → **3b** → **11b**
(*R*)-(–)-carvone → **7** (not **5b**)
(*5R*)-(+)-dihydrocarvone → **8** (not **6b**)

2.1. *10*H*-1,2,3,4-Tetrahydroacridin-9-ones (**I**)*

The synthesis of 10*H*-1,2,3,4-tetrahydroacridin-9-ones **I** and, particularly the unsubstituted derivative (R = H) has been carried out by two methods (Fig. 1). Method A (isolating or not the intermediate Schiff base) was discovered by Tiedke [7] and improved by Reed [8] and Albert [9]. The yields are 40% (R = H), 77% (R = 2-methyl, **1a**, Fig. 2) [8,10] and 37% (**2a**) [8]. We have also used a method inspired in the synthesis of quinolines from cyclohexanones and aminoac-

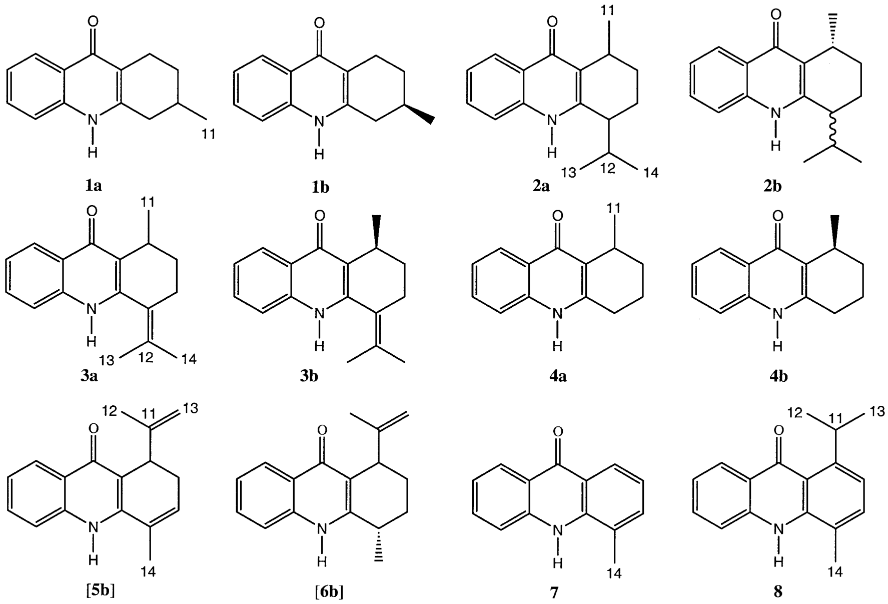


Fig. 2. Tetrahydroacridin-9-ones.

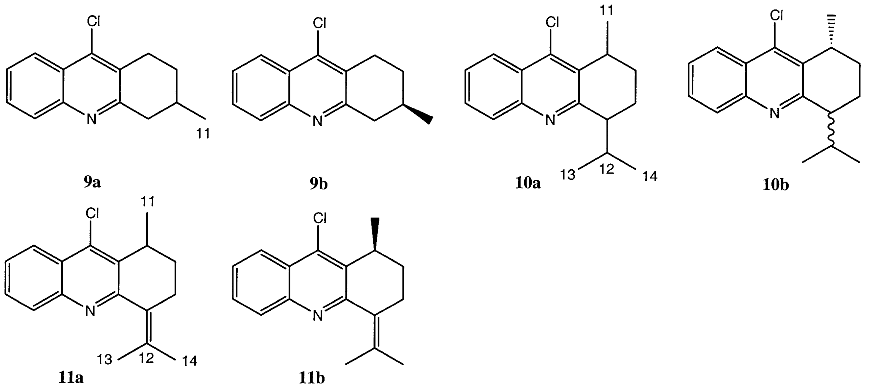


Fig. 3. 9-Chlorotetrahydroacridines.

rolein, in the presence of ammonium acetate [11]. Method B (isolating or not the anil intermediate) was discovered by Sen and Basu [12,13], and improved by Hughes and Lions [14]. The yields on **I** (R = H) vary between 20% and 90% [12], but one must consider that acridinones are high melting, very insoluble compounds difficult to purify. Related to this last method is the preparation of 10-aryltetrahydroacridinones (derived from camphor) [15].

We have summarized in Table 1 the results we have obtained using the above-mentioned classical conditions; they are highly unsatisfactory except in entry 5 (53%, showing the importance of the duration of the third period of heating). We decided then to apply to procedure A (anthranilic acid plus cyclanone) under ultrasonic radiation [16].

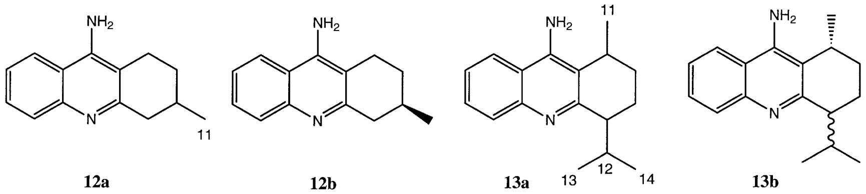
We have used a multimode conventional microwave oven. The conditions best adapted to the physical properties of acridinones are without solvent and without solid support. At the beginning, a sealed Pyrex tube was used (MW1) but, afterwards, the reactions were carried out in a closed mineralization vessel containing an open Pyrex flask topped with a funnel to condense the effluents (MW2). After several essays (not reported), it was found that the best results were obtained with stoichiometric amounts of both reagents. It is important to carry out the heating in several periods of time, open the oven after each period until ambient temperature is restored. For instance, if instead of nine times 1 min (entry 8, Table 1), the vessel was heated continuously for 9 min, only unidentified products were obtained.

With 3-methylcyclohexanone and menthone, either racemic or optically pure, the results were satisfactory improving considerably over the classical conditions. Moreover, the compounds are considerably cleaner and, consequently, easier to purify. In the case of pulegone, the classical conditions (entry 7 and other unreported experiments) lead only to **1a** (identical to that obtained from 3-methylcyclohexanone). In the microwave oven, a mixture of **1, 3** and **4** was obtained (relative amounts 60%–20%–20% determined by integration of some ^{1}H NMR signals in the crude reaction mixture). The origin of these compounds corresponds to the two possible cleavages of the methylethylidene group (Fig. 5).

In the case of (*R*)-(–)-carvone (entries 15 and 16), the desired compound **5b** was not obtained; instead compound **7**

Table 1
Synthesis of 10*H*-1,2,3,4-tetrahydroacridin-9-ones **I** (time in h, temperature *T* in °C)

Entry	Ketone	Method	Time/*T*	Time/*T*	Time/*T*	Product	% yield
1	3-Methylcyclohexanone	A (Ref. [7])	3/120	12/160	2/220	**1a**	24
2	3-Methylcyclohexanone	A (Ref. [12])	22/120			**1a**	5
3	3-Methylcyclohexanone	B (Ref. [14])	2/230			**1a**	9
4	(*R*)-(+)-3-Methylcyclohexanone	A (Ref. [7])	4/120	12/160	3/220	**1b**	14
5	(*R*)-(+)-3-Methylcyclohexanone	A (Ref. [7])	1/120	1/160	12/210	**1b**	53
6	Menthone	A (Ref. [7])	3/120	12/160	2/220	**2a**	14
7	Pulegone	A (Ref. [12])	24/120			**1a**	28
8	3-Methylcyclohexanone	MW1	Nine times 1 min (760 W)			**1a**	74
9	3-Methylcyclohexanone	MW2	Three times 1 min (500 W)			**1a**	61
10	(*R*)-(+)-3-Methylcyclohexanone	MW2	Three times 1 min (500 W)			**1b**	69
11	Menthone	MW2	Five times 2 min (500 W)			**2a**	46
12	(2*S*,5*R*)-(–)-Menthone	MW2	Five times 2 min (500 W)			**2b**	54
13	Pulegone	MW2	Three times 2 min (500 W)			**1a,3a,4a**	29
14	(*R*)-(+)-Pulegone	MW2	Three times 2 min (500 W)			**1b,3b,4b**	35
15	(*R*)-(–)-Carvone	MW1	Five times 3 min (450 W)			**7**	10
16	(*R*)-(–)-Carvone	MW2	Three times 2 min (450 W)			**7**	12
17	(5*R*)-(+)-Dihydrocarvone	MW2	Four times 2 min (450 W)			**8**	6



12a **12b** **13a** **13b**

Fig. 4. 9-Aminotetrahydroacridines.

resulting from the cleavage of the substituent at position 1 followed by aromatization was isolated but with a small yield both with MW1 and MW2 conditions (shorter time). (*5R*)-(+)-Dihydrocarvone affords the aromatized derivative **8** in a very low yield without traces of the expected compound **6b** (see Fig. 2).

2.2. *9-Chlorotetrahydroacridines (**II**)*

Only the six first compounds of Fig. 2 (**1a, 1b, 2a, 2b, 3a, 3b**) have been transformed into the corresponding 9-chloroacridines **9a, 9b, 10a, 10b, 11a** and **11b** (Fig. 3) by reaction with phosphorus oxychloride [8,17]. The following yields have been obtained: **9a** (86%), **9b** (72%), **10a** (68%), **10b** (76%). The mixtures **1a/3a/4a** and **1b/3b/4b** have been treated as such and the desired compounds **11a** and **11b** have been obtained in 26% and 25% yields, respectively.

The good results obtained for compounds **I** using the MW irradiation, prompted us to explore its application to prepare compounds **II**. The yields are lower or similar but the reaction times are much shorter, from 2 h to 30 s: **9a** (62%), **9b** (53%), **10a** (77%), **10b** (83%), **11a** (28%) and **11b** (21%).

2.3. *9-Aminotetrahydroacridines (**III**)*

Only the four compounds on the top of Fig. 4 have been transformed into 9-aminotetrahydroacridines (**III**) (Fig. 4).

Once more, we decided to use the MW irradiation, but in this case with moderate success, the yields were comprised between 12% and 18%, even using solid supports (silica, basic alumina, montmorillonite K10 and KSF).

2.4. *9-(Pyrazol-1-yl)-tetrahydroacridines (**IV**)*

The nucleophilic substitution of the chlorine atom in compounds **II** is also difficult. For instance, Michalson [18] failed to replace it by azetidine. An attempt to react **9a** with pyrazole in phenol does not succeed and the starting compounds were recovered. The use of MW was very successful when the pyrazole is liquid, like 3(5)-methylpyrazole (98% yield of a 2:1 mixture of **15a** and **16a**), because the reagents mixed well but not so with solid pyrazoles, like pyrazole (Mp 66–68 °C, 35% in **14a**) and even less with 3(5)-dimethylpyrazole (Mp 106–108 °C), where no substitution product was isolated, only 3-methylacridinone [19] was recovered (by aromatization of the tetrahydroacridine with concomitant hydrolysis) (see Fig. 6).

2.5. *Characterization of the compounds*

All the compounds were characterized by ^{1}H, ^{13}C NMR (mono and 2D spectra) and by MS. Compounds derived from menthone (**2a, 10a, 13a**) and from (*2S,5R*)-(–)-menthone (**2b, 10b, 13b**) are mixture of diastereoisomers (Fig. 7). Since the NMR spectra of the racemic and the enantiomers are identical, in the experimental part, only those of the former will be reported.

We have been able to grow single crystals of **10b** (Fig. 8): they correspond to the *cis* isomer (*1R,4R*). Therefore, the isopropyl α to the carbonyl of menthone has been epimerized in the first step of the synthesis (formation of **2b**). We have verified that the crystals used for the structure determination correspond to the major isomer *cis*-**10b** (the minor one *trans*-**10b** having the *1R,4S* configuration).

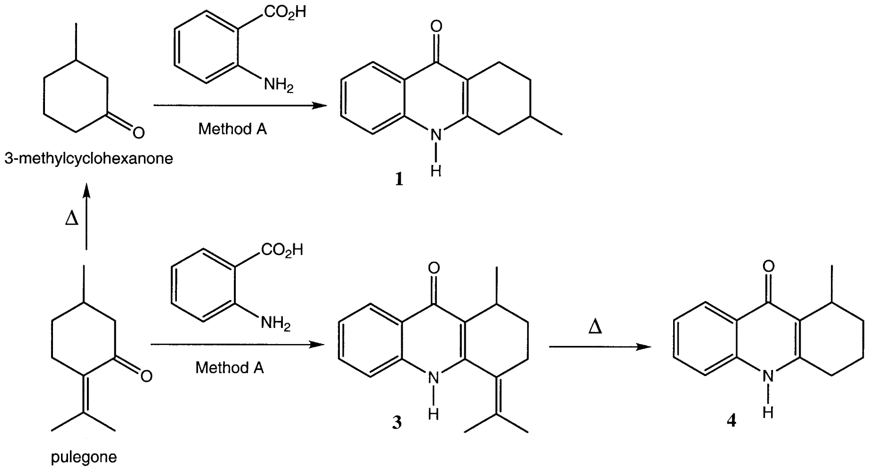
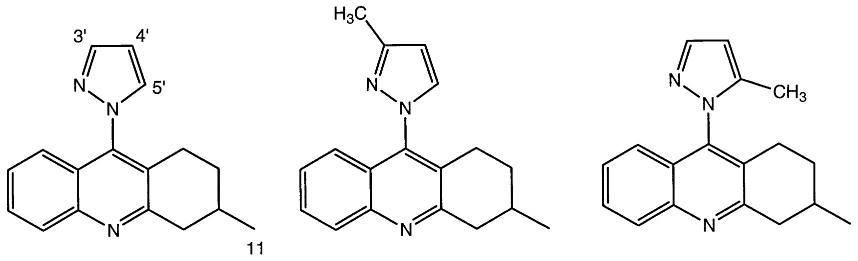


Fig. 5. Compounds obtained from pulegone.



14a **15a** **16a**

Fig. 6. 9-(Pyrazol-1-yl)-tetrahydroacridines.

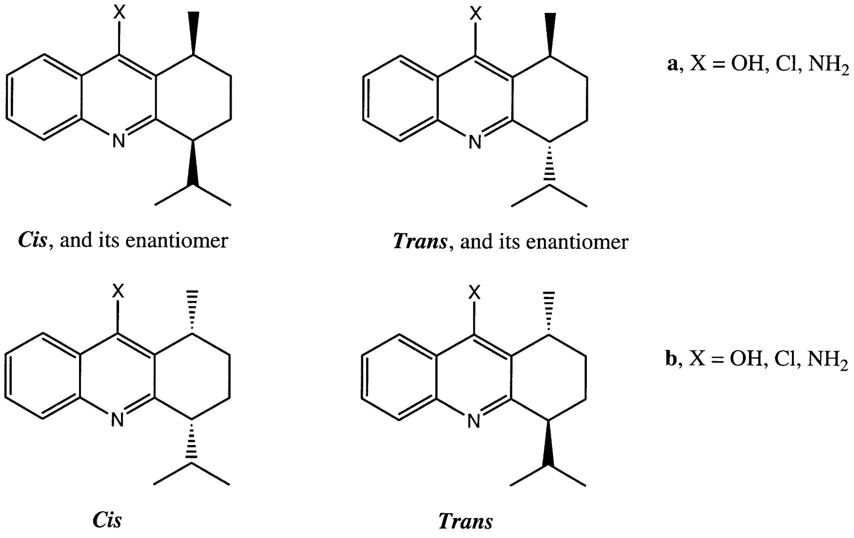
The stereochemistry of the menthone derivatives is based on the relative chemical shifts of H-12, C-3, C-11 and C-12: defining $\Delta\delta$ as δ_{trans}–δ_{cis}, these differences are: **2** (–0.30, +1.09, +0.66, +2.62 ppm), **10** (–0.55, +2.03, +0.97, +2.46 ppm) and **13** (–0.52, +2.12, +0.74, +2.38 ppm). Since all our subsequent discussion will be based on the correct assignment of the *cis/trans* pair of the chloro derivative **10b**, we have carried out GIAO/DFT calculations of the ^{1}H and ^{13}C chemical shifts (see experimental part) on these compounds. The absolute shieldings have been transformed into chemical shifts by means of the shieldings of TMS. The experimental and calculated chemical shifts are compared in Table 2. Carbon C(9) bearing the chlorine atom has been excluded from the comparisons because at this level of the calculations it cannot be reproduced adequately [20].

The agreement is rather satisfactory and the main differences (in bold) between both isomers are well reproduced. However, we have underlined some calculated $\Delta\delta$ (*trans–cis*) that deviate. In the case of ^{1}H NMR (CH$_2$ at position 3, calculated –0.45 and –0.72, experimental +0.44 and +0.05 ppm), it is probably related to the fact that the ABCDEF system (neglecting the couplings with methyl groups) formed by the six protons at positions 1–2–3–4 has not been analyzed. Probably, the calculated values are better than the experimental ones. In the case of ^{13}C NMR, which is very sensitive to the geometry [21], these differences correspond to conformational changes between the minimized structure and the conformationally flexible molecule existing in solution.

We have compared the minimum structure of the *cis* isomer with that determined by X-ray diffraction for compound **10b** (see Table 3): the agreement for the *cis* compound is very satisfactory, indicating that it should have a restricted mobility. The less stable *trans* isomer, is very different and probably the anomalies arise from it. When the experimental and calculated chemical shifts of Table 2 are compared, the differences are much smaller for the *cis* than for the *trans* isomer, especially regarding saturated carbons (range: *cis* 2.2 ppm, *trans* 10.6 ppm).

We have summarized in Fig. 9, the sequences of transformations, together with the NMR most significant chemical shifts and some AM1 calculations.

In the first step, since the total yield is 54%, we have verified, by ^{1}H NMR, that the crude product contains between 65% and 70% of the *cis* isomer (depending on the experimental conditions). The most reasonable explanation is that epimerization occurs on the starting menthone. The second step occurs with high yield and the *cis/trans* ratio is almost the same, so, it is not necessary to assume any equilibration. However, when the sample from X-ray crystallogra-



a, X = OH, Cl, NH$_2$

Cis, and its enantiomer

Trans, and its enantiomer

b, X = OH, Cl, NH$_2$

Cis

Trans

Fig. 7. Diastereoisomers derived from menthone.

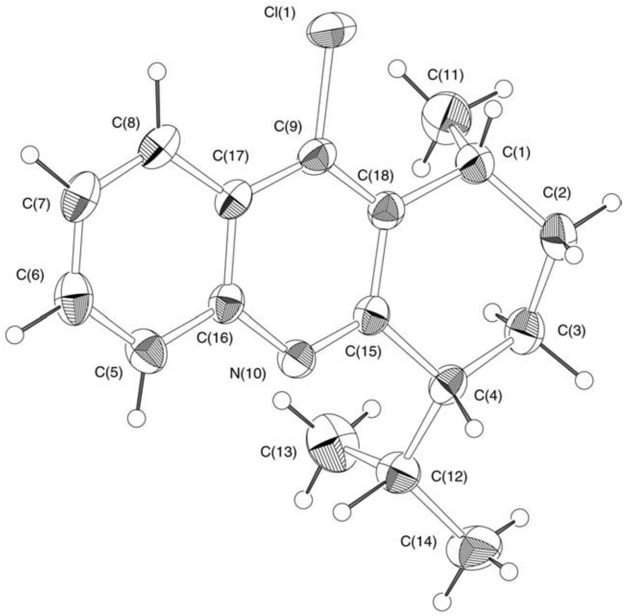


Fig. 8. An ORTEP view of the molecule *cis*-**10b**.

phy (pure *cis*-**10b**) is heated in the NMR tube for 3 days at 78 °C, epimerization occurs (*cis/trans* ratio 80:20). The yield in compound **13** (obtained from anthanilonitrile and menthone) is very low (15%); in this case it seems that the epimerization is less important although the complexity of the crude hinders the confirmation of *cis/trans* ratio.

Concerning the tautomerism of structures **I** and **III**, we do not provide new information concerning the oxo/hydroxy tautomerism of **I**, but it is safe to assume that in solution they exist in the oxo form as represented [22]. In the case of the amino/imino tautomerism of **III**, unpublished results on related compounds pointed out that the amino tautomer (represented) predominate in $CDCl_3$ solution whereas the imino one is favored in DMSO solution. The structural criteria is easily described: aminoacridines resemble acridines and C5 appears at ~130 ppm while iminoacridines resemble acridanones and C5 appears at ~120 ppm. In compound **12a**, in $CDCl_3$, solution C5 resonates at 128.87 ppm (amine) while in compound **13a** this carbon appears at 119.94 ppm in DMSO-d_6 (imine).

The 9-pyrazolyl-3-methyl-1,2,3,4-tetrahydroacridines show in ^1H NMR the shielding of the protons of the CH_2 group at position 1 due to the anisotropy of the 9-aromatic residue (thus proving that this substituent is out of plane). According to AM1 calculations, the dihedral angle is $\phi = 60°$ for compounds **14a** and **15a** and $\phi = 75°$ for compound **16a** (always with the lone pair pointing towards the saturated ring, see Fig. 10). For the first two compounds, there is free rotation about the C9-N1′ bond but for the last one, the planar transition state ($\phi = 0°$) is hindered by the 5′-methyl group and both atropisomers (diastereoisomers due to the 3-methyl group) are observed in some ^1H and most ^{13}C NMR signals.

2.6. Conclusion

Twenty-two new compounds related to tacrine have been prepared, in several cases, classical heating has been replaced successfully by the use of MW methodology, which increases the yields and affords products easier to purify. Although the characterization is based mainly in the extensive use of mono and 2D NMR methods, the relative configuration of the 1 and 4 positions of menthone derivatives was determined by X-ray crystallography (compound *cis*-**10b**). Due to importance of these compounds, theoretical calculations at the GIAO/B3LYP/6-31G* level were carried out. The chemical shifts calculated for *cis*-**10b** and *trans*-**10b** are very close to those determined experimentally, and the few references observed have been assigned to conformational differences in the *trans* isomer. One of the pyrazole derivatives, 9-(5-methylpyrazol-1-yl)-3-methyl-1,2,3,4-tetrahydroacridine (**15a**), presents atropisomerism.

3. Experimental section

3.1. General procedures

Melting points (Electrothermal 9300) are uncorrected. ^1H spectra were recorded at 200, 400 and 500 MHz, and ^{13}C NMR spectra were recorded at 50.3, 100.6 and 126 MHz. ^1H and ^{13}C chemical shifts were measured in ppm relative to internal Me_4Si, and coupling constants are expressed in Hz. Assignments were based on a series of mono and bidimensional experiments including gs-COSY, gs-HMQC and gs-HMBC. The proportions of the mixtures of diastereoisomers have been determined by ^1H NMR at 500 MHz, generally on the signals of the methyl groups. A domestic microwave oven, Bluesky® WD 800 EL25, released power 800 W, frequency 2450 MHz, was used in this work. The reactions were carried out in a mineralization vessel Rotilabo® ref. A352.1 from Roth, capacity 120 ml, built in PFA. The optical rotation angles α (10^{-1} deg cm^3 g^{-1}) were determined in methanol at 20 °C using a Perkin-Elmer 343 polarimeter.

3.2. 10H-*1,2,3,4-Tetrahydroacridin-9-ones: classical methods*

Method A (Ref. [7]), applied to 3-methylcyclohexanone (entry 1, Table 1), to (*R*)-(+)-3-methylcyclohexanone (entries 4 and 5, Table 1) and to menthone (entry 6, Table 1). A mixture of the ketone (0.026 mol) and anthranilic acid (3.57 g, 0.026 mol) in a round bottom flask are heated *m* h at 120 °C, then *n* h at 160 °C and finally *o* h at 210–220 °C (see Table 1 for *m, n* and *o*). The black solid is treated with diethyl ether until it became a yellow–gray solid, ether is removed and the compound dried in an oven.

Method A (Ref. [11]), applied to 3-methylcyclohexanone (entry 2, Table 1) and to pulegone (entry 7, Table 1). A mixture of ketone (0.027 mol), anthranilic acid (3.57 g,

Table 2
Comparison of experimental and calculated chemical shifts (*δ* ppm) of compounds *cis*-**10** and *trans*-**10**

Compound	Atom	^{1}H experimental	Δ*δ* (*trans–cis*)	^{1}H calculated	Δ*δ* (*trans–cis*)	^{13}C experimental	Δ*δ* (*trans–cis*)	^{13}C calculated	Δ*δ* (*trans–cis*)
cis-**10**	1 (CH)	3.53	0.07	3.49	0.08	30.98	–0.15	31.66	–0.60
	2 (CH_2)	1.86	0.44	1.87	0.52	28.67	–1.66	28.34	2.91
	2 (CH_2)	1.86	0.44	2.00	–0.45	–	–	–	–
	3 (CH_2)	1.86	0.05	2.13	–0.72	16.68	**2.03**	17.97	4.99
	3 (CH_2)	1.86	0.05	1.72	0.20	–	–	–	–
	4 (CH)	3.01	–0.11	3.11	–0.28	47.54	0.39	45.31	0.58
	4a (q)	–	–	–	–	162.00	0.04	162.82	0.41
	5a (q)	–	–	–	–	147.12	0.55	147.05	–0.90
	5 (CH)	7.96	0.03	7.84	0.05	129.10	0.00	129.71	0.08
	6 (CH)	7.63	0.00	7.57	0.01	129.10	0.00	127.75	–0.05
	7 (CH)	7.50	0.00	7.47	0.01	126.52	0.00	125.72	–0.10
	8 (CH)	8.15	0.02	8.06	0.02	123.94	–0.05	123.94	–0.17
	8a (q)	–	–	–	–	125.18	–0.36	125.21	0.32
	9 (C–Cl)	–	–	–	–	140.96	–	–	–
	9a (q)	–	–	–	–	134.41	0.28	134.80	0.05
	11 (CH_3)	1.31	–0.05	1.35 [a]	–0.05	19.75	**0.97**	19.73	**2.83**
	12 (CH)	3.18	**–0.55**	3.57	**–0.46**	30.61	**2.46**	29.70	–1.02
	13 (CH_3)	0.66	0.10	0.76 [a]	0.10	16.71	**2.38**	15.93	**2.09**
	14 (CH_3)	1.10	–0.05	1.16 [a]	–0.03	20.82	0.90	20.49	0.42
trans-**10**	1 (CH)	3.60		3.57		30.83		31.06	
	2 (CH_2)	2.30		2.39		27.01		31.24	
	2 (CH_2)	2.30		1.55		–		–	
	3 (CH_2)	1.91		1.41		18.71		22.95	
	3 (CH_2)	1.91		1.92		–		–	
	4 (CH)	2.90		2.83		46.13		45.89	
	4a (q)	–		–		161.96		163.23	
	5a (q)	–		–		146.57		146.15	
	5 (CH)	7.99		7.89		129.10		129.79	
	6 (CH)	7.63		7.58		129.10		127.70	
	7 (CH)	7.50		7.48		126.52		125.61	
	8 (CH)	8.17		8.08		123.99		123.77	
	8a (q)	–		–		125.54		125.53	
	9 (C–Cl)	–		–		140.71		–	
	9a (q)	–		–		134.13		134.85	
	11 (CH_3)	1.26		1.30 [a]		20.72		22.95[a]	
	12 (CH)	2.63		3.11		33.07		28.68	
	13 (CH_3)	0.76		0.78 [a]		19.09		18.02[a]	
	14 (CH_3)	1.05		1.13 [a]		21.72		20.91[a]	

[a] The absolute shieldings of the three protons of the methyl groups have been averaged.

0.026 mol) and ammonium acetate (3 mg) is heated at 120 °C during 22 h. The solid is treated with diethyl ether until it became a yellow–gray solid, ether is removed and the compound dried in an oven.

Method B (Ref. [12]), applied to 3-methylcyclohexanone (entry 3, Table 1). A mixture of the β-ketoester (see Fig. 1) (0.027 mol) and aniline (2.51 g, 0.027 mmol) are set in a desiccator for 8 days (formation of crystals). The mixture is heated at 230 °C for 2 h. The residue is treated with a 50:50 mixture of ether and petrol ether, and the solid is filtered and dried.

*3.3. 10*H*-1,2,3,4-Tetrahydroacridin-9-ones: microwave method*

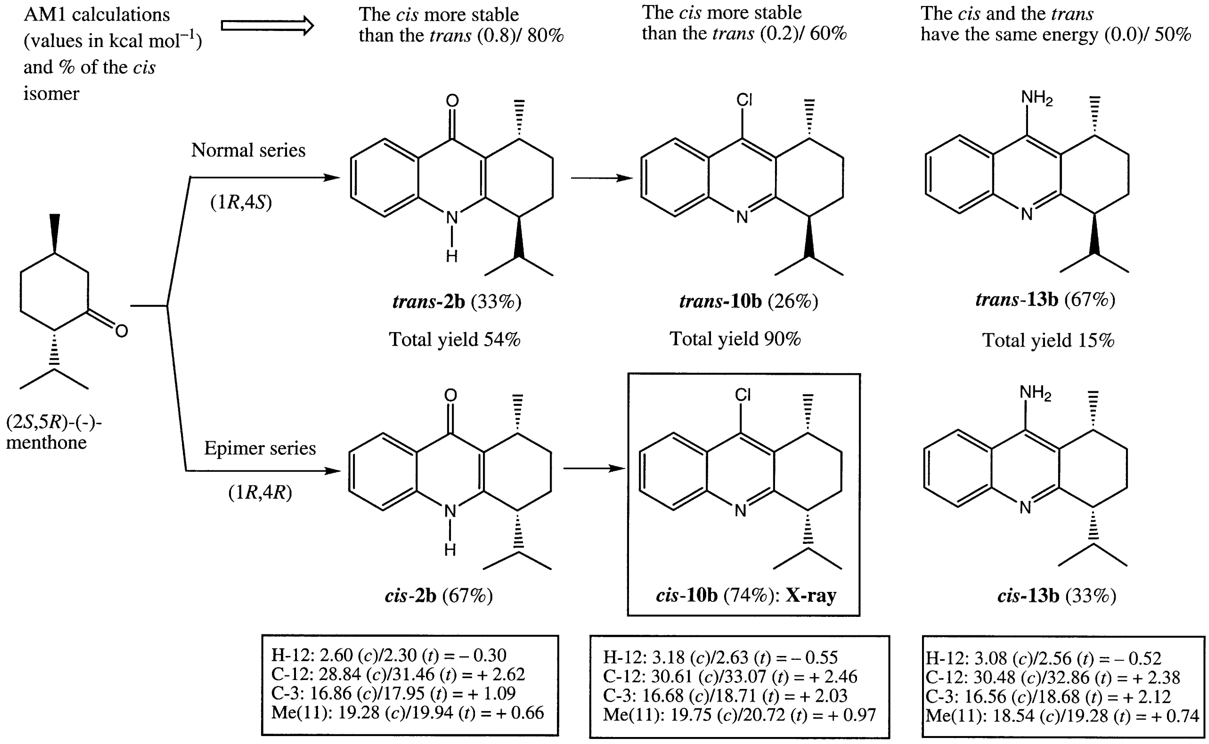
Method MW1, applied to 3-methylcyclohexanone (entry 8, Table 1) and to (*R*)-(–)-carvone (entry 15, Table 1). Anthranilic acid (3.57 g, 0.026 mol) is dissolved in the ketone (0.026 mol) and sealed in a Pyrex tube. After the power and time reported in Table 1 were applied, the tube is cooled and opened. The maroon solid is treated with 5 ml of diisopropylether. The solid is filtered and dried on an oven.

Method MW2 (applied to entries 9–14 and 16, 17 of Table 1). Anthranilic acid (3.57 g, 0.026 mol) is dissolved in

Table 3
Torsion angles (τ°) of the saturated part of compounds *cis*-**10** and *trans*-**10**

Atoms [a]	τ (experimental)	τ (calculated *cis*) [b]	τ (calculated *trans*) [b]
C(4)–C(15)–C(18)–C(1)	3.5	4.3	–7.1
C(15)–C(18)–C(1)–C(2)	–22.3	–24.9	17.3
C(18)–C(1)–C(2)–C(3)	51.8	53.3	14.7
C(1)–C(2)–C(3)–C(4)	–64.0	–62.1	–55.5
C(2)–C(3)–C(4)–C(15)	42.7	39.2	64.1
C(3)–C(4)–C(15)–C(18)	–13.5	–11.3	–33.4
C(13)–C(12)–C(4)–C(3)	–67.9	–65.7	–53.7
C(14)–C(12)–C(4)–C(3)	57.7	60.5	72.0

[a] See Fig. 1 for the atoms numbering.
[b] B3LYP/6-31G*.



H-12: 2.60 (*c*)/2.30 (*t*) = – 0.30
C-12: 28.84 (*c*)/31.46 (*t*) = + 2.62
C-3: 16.86 (*c*)/17.95 (*t*) = + 1.09
Me(11): 19.28 (*c*)/19.94 (*t*) = + 0.66

H-12: 3.18 (*c*)/2.63 (*t*) = – 0.55
C-12: 30.61 (*c*)/33.07 (*t*) = + 2.46
C-3: 16.68 (*c*)/18.71 (*t*) = + 2.03
Me(11): 19.75 (*c*)/20.72 (*t*) = + 0.97

H-12: 3.08 (*c*)/2.56 (*t*) = – 0.52
C-12: 30.48 (*c*)/32.86 (*t*) = + 2.38
C-3: 16.56 (*c*)/18.68 (*t*) = + 2.12
Me(11): 18.54 (*c*)/19.28 (*t*) = + 0.74

Fig. 9. Diastereoisomers derived from (2*S*,5*R*)-(–)-menthone.

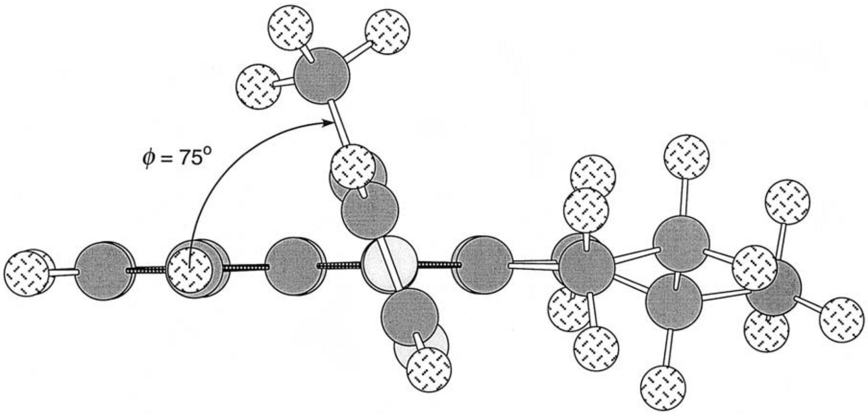


Fig. 10. A schematic view of **16a** along the C9-N1′ bond.

the ketone (0.026 mol), put a Pyrex tube within a mineralization bomb. The conditions of Table 1 were applied and the residue treated as previously. The yields of the different methods are reported in Table 1.

3.4. *3-Methyl-10*H*-1,2,3,4-tetrahydroacridin-9-one (**1a**)*

Mp >320 °C. HRMS (EI) calcd for $C_{14}H_{15}NO$ 213.11536, found 213.11521. ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 3H, J = 6.4, H-11), 1.28 (dq, 1H, J = 11.6, 5.8, H-2a), 1.84 (m, 2H, H-2b and H-3), 2.30 (ddd, 1H, J = 16.8, 10.9, 6.2, H-1a), 2.36 (dd, 1H, J = 17.2, 10.2, H-4a), 2.66 (dm, 1H, J = 17.2, H-1b), 2.73 (dd, 1H, J = 16.8, 4.9, H-4b), 7.21 (t, 1H, J = 7.5, H-7), 7.45 (d, 1H, J = 8.2, H-5), 7.56 (t, 1H, J = 7.5, H-6), 8.04 (d, 1H, J = 8.0, H-8), 11.39 (br, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 21.12 (C-11), 21.54 (C-1), 27.68 (C-3), 30.04 (C-2), 35.23 (C-4), 115.11 (C-9a), 117.38 (C-5), 121.97 (C-7), 123.31 (C-8a), 124.85 (C-8), 132.92 (C-6), 139.26 (C-5a), 146.38 (C-4a), 175.88 (C-9).

3.5. *(*R*)-3-Methyl-10*H*-1,2,3,4-tetrahydroacridin-9-one (**1b**)*

Mp >320 °C. HRMS (EI) calcd for $C_{14}H_{15}NO$ 213.11536, found 213.11544.

3.6. *1-Methyl-4-isopropyl-10*H*-1,2,3,4-tetrahydroacridin-9-one (**2a**)*

Mp = 265 °C. HRMS (EI) calcd for $C_{17}H_{21}NO$ 255.16231, found 255.16209. Major diastereoisomer (67%): ^{1}H NMR (DMSO-d_6) δ 0.66 (d, 3-H, J = 6.7, H-13), 1.04 (d, 3H, J = 6.7, H-14), 1.12 (d, 3H, J = 6.9, H-11), 1.61 (m, 2H, H-3), 1.68 (m, 2H, H-2), 2.60 (o, 1H, J = 6.6, H-12), 2.78 (td, 1H, J = 8.3, 5.0, H-4), 3.08 (m, 1H, H-1), 7.20 (t, 1H, J = 7.6, H-7), 7.54 (t, 1H, J = 7.6, H-6), 7.61 (d, 1H, J = 8.3, H-5), 8.05 (d, 1H, J = 8.0, H-8), 10.85 (s, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 15.96 (C-13), 16.86 (C-3), 19.28 (C-11), 20.26 (C-14), 25.40 (C-1), 27.72 (C-2), 28.84 (C-12), 41.34 (C-4), 117.68 (C-5), 121.95 (C-7), 122.21 (C-9a), 123.18 (C-8a), 124.90 (C-8), 130.89 (C-6), 139.61 (C-5a), 148.91 (C-4a), 175.69 (C-9). Minor diastereoisomer (33%): ^{1}H NMR (DMSO-d_6) δ 0.82 (d, 3H, J = 6.9, H-13), 1.01 (d, 3H, J = 6.8, H-14), 1.09 (d, 3H, J = 6.8, H-11), 1.68 (m, 2H, H-2), 1.82 (m, 2H, H-3), 2.30 (o, 1H, J = 6.6, H-12), 2.56 (m, 1H, H-4), 3.08 (m, 1H, H-1), 7.20 (t, 1H, J = 7.6, H-7), 7.54 (t, 1H, J = 7.6, H-6), 7.61 (d, 1H, J = 8.3, H-5), 8.06 (d, 1H, J = 8.0, H-8), 10.98 (s, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 17.95 (C-3), 19.42 (C-13), 19.94 (C-11), 21.80 (C-14), 25.43 (C-1), 26.49 (C-2), 31.46 (C-12), 41.00 (C-4), 117.52 (C-5), 121.36 (C-9a), 121.88 (C-7), 123.38 (C-8a), 124.80 (C-8), 130.89 (C-6), 139.27 (C-5a), 148.61 (C-4a), 175.65 (C-9).

3.7. *(1*R*)-(+)-1-Methyl-4-isopropyl-10*H*-1,2,3,4-tetrahydroacridin-9-one (**2b**)*

Mp = 266 °C. HRMS (EI) calcd for $C_{17}H_{21}NO$ 255.16231, found 255.16209. $[\alpha]^{20}_D$ = +2.2 (c = 1.0, MeOH).

3.8. *1-Methyl-4-(1-methylethylidene)-10*H*-1,2,3,4-tetrahydroacridin-9-one (**3a**)*

HRMS (EI) calcd for $C_{17}H_{19}NO$ 253.14666, found 253.14691. ^{1}H NMR (DMSO-d_6) δ 1.05 (d, 3H, J = 6.4, H-11), 1.60 (m, 2H, H-2), 1.89 (s, 3H, H-14), 2.60 (m, 2H, H-3), 3.22 (hex, 1H, J = 6.4, H-1), 7.22 (t, 1H, J = 7.5, H-7), 7.45 (d, 1H, J = 8.2, H-5), 7.58 (t, 1H, J = 7.4, H-6), 8.06 (d, 1H, J = 8.0, H-8), 10.86 (br, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 19.60 (C-11), 21.67 (C-13), 22.78 (C-14), 25.33 (C-3), 25.81 (C-1), 30.51 (C-2), 118.00 (C-5), 122.15 (C-9a), 122.18 (C-7), 123.93 (C-8a), 124.96 (C-8), 126.11 (C-12), 130.83 (C-6), 133.31 (C-4), 138.99 (C-4a), 145.25 (C-5a), 174.99 (C-9).

3.9. *(*R*)-1-Methyl-4-(1-methylethylidene)-10*H*-1,2,3,4-tetrahydroacridin-9-one (**3b**)*

HRMS (EI) calcd for $C_{17}H_{19}NO$ 253.14666, found 253.14657.

3.10. *1-Methyl-10*H*-1,2,3,4-tetra-hydroacridin-9-one (**4a**)*

HRMS (EI) calcd for $C_{14}H_{15}NO$ 213.11536, found 213.11497. ^{1}H NMR (DMSO-d_6) δ 1.12 (d, 3H, J = 6.8, H-11), 1.61 (m, 1H, H-2a), 1.68 (m, 1H, H-2b), 1.78 (m, 1H, H-3a), 1.84 (m, 1H, H-3b), 2.66 (m, 2H, H-4), 0.22 (hex, 1H, J = 6.2, H-1), 7.21 (t, 1H, J = 7.5, H-7), 7.44 (d, 1H, J = 8.2, H-5), 7.56 (t, 1H, J = 7.4, H-6), 8.04 (d, 1H, J = 8.0, H-8), 11.28 (br, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 16.94 (C-3), 19.64 (C-11), 25.41 (C-1), 27.29 (C-4), 30.51 (C-2), 117.27 (C-5), 120.36 (C-9a), 121.89 (C-7), 123.68 (C-8a), 124.85 (C-8), 130.92 (C-6), 139.26 (C-5a), 146.38 (C-4a), 175.78 (C-9).

3.11. *(*R*)-1-Methyl-10*H*-1,2,3,4-tetrahydroacridin-9-one (**4b**)*

HRMS (EI) calcd for $C_{14}H_{11}NO$ 213.11536, found 213.11512.

3.12. *4-Methyl-10*H*-1,2-dihydroacridin-9-one (**7**)*

Mp 315 °C. HRMS (EI) calcd for $C_{17}H_{17}NO$ 209.24328, found 209.24315. ^{1}H NMR (DMSO-d_6) δ 2.60 (s, 3H, H-14), 7.16 (t, 1H, J = 7.3, H-2), 7.26 (t, 1H, J = 7.3, H-7), 7.57 (d, 1H, J = 6.7, H-3), 7.72 (t, 1H, J = 7.3, H-6), 7.96 (d, 1H, J = 8.3, H-5), 8.12 (d, 1H, J = 7.8, H-1), 8.21 (d, 1H, J = 7.8, H-8), 10.66 (br, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 18.03 (C-14), 118.32 (C-5), 120.44 (C-8a), 120.80 (C-2 and C-9a), 121.34 (C-7), 124.03 (C-1), 125.45 (C-4), 125.82 (C-8), 133.28 (C-6), 134.19 (C-3), 139.64 (C-4a), 141.23 (C-5a), 177.52 (C-9).

3.13. *4-Methyl-1-isopropyl-10*H*-acridin-9-one (**8**)*

Mp 129 °C. HRMS (EI) calcd for $C_{17}H_{17}NO$ 251.13101, found 251.13113. ^{1}H NMR (DMSO-d_6) δ 1.23 (d, 6H, J = 6.6, H-12 and H-13), 2.50 (s, 3H, H-14), 4.86 (hex, 1H, J = 6.6, H-11), 7.11 (d, 1H, J = 7.4, H-2), 7.22 (t, 1H, J = 7.2, H-7), 7.48 (d, 1H, J = 7.3, H-3), 7.67 (t, 1H, J = 7.4, H-6), 7.88 (d, 1H, J = 8.2, H-5), 8.18 (d, 1H, J = 7.7, H-8), 10.21

(br, 1H, H-10); ^{13}C NMR (DMSO-d_6) δ 18.21 (C-14), 24.28 (C-12 and C-13), 28.42 (C-11), 117.61 (C-5), 117.69 (C-9a), 118.00 (C-2), 121.11 (C-8a), 122.05 (C-4), 122.56 (C-7), 126.17 (C-8), 132.85 (C-6), 133.71 (C-3), 140.12 (C-5a), 141.06 (C-4a), 149.43 (C-1), 179.18 (C-9).

3.14. 9-Chloro-1,2,3,4-tetrahydroacridines

3.14.1. Classical method

The corresponding 1,2,3,4-tetrahydro-acridinone (**I**) (3 g) are dissolved in a large excess of phosphorus oxychloride (10 equivalents) and heated at 120 °C during 2–3 h. The mixture is poured into a mixture of water and ice and the pH raised to 12 adding ammonia. The solution is extracted three times with 30 ml of chloroform, the organic layers dried over magnesium sulfate and evaporated. The residuals are chromatographed on silica gel (CH_2Cl_2/AcOEt 80:20).

3.14.2. Microwave method

The corresponding 1,2,3,4-tetrahydro-acridinone (**I**) (3 g) are dissolved in phosphorus oxychloride (2.5 equivalents) and placed in a Pyrex flask inside a mineralization vessel. The heating (900 W) was 30 s. Phosphorus oxychloride was evaporated under reduced pressure and the residue mixed with 5 ml of ice water. The aqueous solution is extracted three times with 10 ml of chloroform, the organic layers dried over magnesium sulfate and evaporated. The residuals are chromatographed on silica gel (CH_2Cl_2/AcOEt 80:20).

3.15. 9-Chloro-3-methyl-1,2,3,4-tetrahydroacridine (*9a*)

Yields 86% (classical) and 62% (MW). Mp 59 °C. HRMS (EI) calcd for $C_{14}H_{14}ClN$ 231.72040, found 231.72038. ^{1}H NMR (DMSO-d_6) δ 1.06 (d, 3H, *J* = 6.3, H-11), 1.32 (dq, 1H, *J* = 11.8, 5.9, H-2a), 1.90 (m, 1H, H-3), 1.92 (m, 1H, H-2b), 2.60 (dd, 1H, *J* = 17.2, H-4a), 2.72 (ddd, 1H, *J* = 17.7, 11.1, 6.1, H-1a), 3.04 (ddd, 1H, *J* = 17.7, 5.4, 3.0, H-1b), 3.11 (dm, 1H, *J* = 17.2, H-4b), 7.42 (t, 1H, *J* = 7.4, H-7), 7.56 (t, 1H, *J* = 7.5, H-6), 7.90 (d, 1H, *J* = 8.3, H-5), 8.03 (d, 1H, *J* = 8.3, H-8); ^{13}C NMR (DMSO-d_6) δ 21.38 (C-11), 26.92 (C-1), 28.68 (C-2), 30.45 (C-3), 42.30 (C-4), 123.43 (C-8), 125.12 (C-8a), 126.28 (C-7), 128.06 (C-9a), 128.48 (C-6), 129.03 (C-5), 141.09 (C-9), 146.53 (C-5a), 159.03 (C-4a).

3.16. (R)-9-Chloro-3-methyl-1,2,3,4-tetrahydroacridine (*9b*)

Yields 72% (classical) and 42% (MW). Mp 57 °C. HRMS (EI) calcd for $C_{14}H_{14}ClN$ 231.72040, found 251.72017.

3.17. 9-Chloro-1-methyl-4-isopropyl-1,2,3,4-tetrahydroacridine (*10a*)

Yields 69% (classical) and 79% (MW). Mp 63 °C. HRMS (EI) calcd for $C_{17}H_{20}ClN$ 273.12843, found 273.12830. Major diastereoisomer (74%): ^{1}H NMR ($CDCl_3$) δ 0.66 (d, 3H, *J* = 6.7, H-13), 1.10 (d, 3H, *J* = 7.0, H-14), 1.31 (d, 3H, *J* = 6.9, H-11), 1.86 (m, 4H, H-2 and H-3), 3.01 (m, 1H, H-4), 3.18 (o, 1H, *J* = 6.7, H-12), 3.53 (m, 1H, H-1), 7.50 (t, 1H, *J* = 7.6, H-7), 7.63 (t, 1H, *J* = 7.6, H-6), 7.96 (d, 1H, *J* = 8.4, H-5), 8.15 (d, 1H, *J* = 8.1, H-8); ^{13}C NMR ($CDCl_3$) δ 16.68 (C-3), 16.71 (C-13), 19.75 (C-11), 20.82 (C-14), 28.67 (C-2), 30.61 (C-12), 30.98 (C-1), 47.54 (C-4), 123.94 (C-8), 125.18 (C-8a), 126.52 (C-7), 129.10 (C-5 and C-6), 134.41 (C-9a), 140.96 (C-9), 147.12 (C-5a), 162.00 (C-4a). Minor diastereoisomer (26%): ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, *J* = 6.7, H-13), 1.05 (d, 3H, *J* = 6.8, H-14), 1.26 (d, 3H, *J* = 7.0, H-11), 1.91 (m, 2H, H-3), 2.30 (m, 2H, H-2), 2.63 (o, 1H, *J* = 6.6, H-12), 2.90 (m, 1H, H-4), 3.60 (m, 1H, H-1), 7.50 (t, 1H, *J* = 7.6, H-7), 7.63 (t, 1H, *J* = 7.6, H-6), 7.99 (d, 1H, *J* = 8.4, H-5), 8.17 (d, 1H, *J* = 8.0, H-8); ^{13}C NMR ($CDCl_3$) δ 18.71 (C-3), 19.09 (C-14), 20.72 (C-11), 21.72 (C-13), 27.01 (C-2), 30.83 (C-1), 33.07 (C-12), 46.13 (C-4), 123.99 (C-8), 125.54 (C-8a), 126.52 (C-7), 129.10 (C-5 and C-6), 134.13 (C-9a), 140.71 (C-9), 146.67 (C-5a), 161.96 (C-4a).

3.18. (1R)-(+)-9-Chloro-1-methyl-4-isopropyl-1,2,3,4-tetrahydroacridine (*10b*)

Yields 86% (classical) and 90% (MW). Mp 62 °C. HRMS (EI) calcd for $C_{17}H_{20}ClN$ 273.12843, found 273.12865. $[\alpha]^{20}{}_{D}$ = 12.0 (*c* = 1.0, MeOH).

3.19. 9-Chloro-1-methyl-4-(1-methylethylidene)-1,2,3,4-tetrahydroacridine (*11a*)

Yields 26% (classical) and 28% (MW). Liquid. HRMS (EI) calcd for $C_{17}H_{18}ClN$ 271.11278, found 271.11313. ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, *J* = 7.1, H-11), 1.77 (dddd, 1H, *J* = 13.6, 11.8, 7.1, 4.3, H-2a), 1.92 (ddt, 1H, *J* = 13.6, 6.6, 2.6, H-2b), 1.93 (s, 3H, H-13), 2.21 (s, 3H, H-14), 2.61 (brdd, 1H, *J* = 16.0, 6.2, H-3a), 2.79 (brddd, 1H, *J* = 16.0, 13.0, 6.9, H-3b), 3.67 (dq, 1H, *J* = 7.1, 4.1, H-1), 7.52 (brdd, 1H, *J* = 8.2, 7.0, H-7), 7.63 (ddd, 1H, *J* = 8.1, 7.0, 1.4, H-6), 8.00 (brd, 1H, *J* = 8.0, H-5), 8.15 (brd, 1H, *J* = 8.2, H-8); ^{13}C NMR ($CDCl_3$) δ 17.28 (C-11), 22.99 (C-13), 23.60 (C-14), 24.75 (C-3), 28.37 (C-2), 31.45 (C-1), 123.99 (C-8), 124.97 (C-8a), 126.58 (C-7), 127.53 (C-12), 128.96 (C-6), 129.30 (C-5), 135.49 (C-9a), 138.24 (C-4), 138.32 (C-9), 146.59 (C-5a), 157.02 (C-4a).

3.20. (R)-9-Chloro-1-methyl-4-(1-methylethylidene)-1,2,3,4-tetrahydroacridine (*11b*)

Yields 25% (classical) and 21% (MW). Liquid. HRMS (EI) calcd for $C_{17}H_{18}ClN$ 271.11278, found 271.11391.

3.21. 9-Amino-1,2,3,4-tetrahydroacridines

Anthranilonitrile (3.19 g, 0.027 mol), 3-methylcyclohexanone (3.03 g, 0.027 mol) and 5 g of alumina are carefully mixed and placed in a Pyrex flask inside a mineralization vessel. The heating (900 W) was two times 2 min. After cooling, the residue was extracted with 20 ml of CH_2Cl_2, the alumina filtered off, the solvent evaporated and the residue chromatographed (silica gel, first AcOEt, then AcOEt + 2% ammonia).

3.22. *9-Amino-5-methyl-1,2,3,4-tetrahydroacridine (**12a**)*

Yield 14%. Mp 198 °C. HRMS (EI) calcd for $C_{14}H_{16}N_2$ 212.13135, found 212.13149. ^{1}H NMR (DMSO-d_6) δ 1.14 (d, 3H, J = 6.6, H-11), 1.54 (dtd, 1H, J = 13.0, 10.8, 6.2, H-2a), 2.01 (m, 1H, H-3), 2.08 (m, 1H, H-2b), 2.61 (ddd, 1H, J = 16.1, 10.7, 6.2, H-1a), 2.66 (dd, 1H, J = 17.2, 10.7, H-4a), 2.72 (ddd, 1H, J = 15.9, 6.2, 3.2, H-1b), 3.12 (ddd, 1H, J = 17.0, 4.6, 2.0, H-4b), 7.38 (ddd, 1H, J = 8.4, 6.8, 1.2, H-7), 7.58 (ddd, 1H, J = 8.5, 6.8, 1.2, H-6), 7.71 (d, 1H, J = 8.3, H-8), 7.91 (d, 1H, J = 8.5, H-5); ^{13}C NMR (DMSO-d_6) δ 21.61 (C-11), 23.45 (C-1), 28.99 (C-3), 30.76 (C-2), 42.46 (C-4), 109.98 (C-9a), 117.21 (C-8a), 119.66 (C-8), 123.98 (C-7), 128.54 (C-6), 128.87 (C-5), 146.71 (C-5a), 158.51 (C-4a).

3.23. *(*R*)-9-Amino-5-methyl-1,2,3,4-tetrahydroacridine (**12b**)*

Yield 18%. Mp 199–200 °C. HRMS (EI) calcd for $C_{14}H_{16}N_2$ 212.13135, found 212.13162.

3.24. *9-Amino-1-methyl-4-isopropyl-1,2,3,4-tetrahydroacridine (**13a**)*

Yield 13%. Mp 100–102 °C. HRMS (EI) calcd for $C_{17}H_{22}N_2$ 254.17830, found 254.17817. Major diastereoisomer (67%): ^{1}H NMR (CDCl$_3$) δ 0.74 (d, 3H, J = 6.9, H-13), 1.01 (d, 3H, J = 6.9, H-14), 1.18 (d, 3H, J = 7.1, H-11), 1.75 (m, 2H, H-3), 2.01 (m, 2H, H-2), 2.56 (o, 1H, J = 6.6, H-12), 2.79 (m, 1H, H-4), 3.02 (m, 1H, H-1), 7.30 (t, 1H, J = 7.5, H-7), 7.50 (t, 1H, J = 7.6, H-6), 7.68 (d, 1H, J = 8.2, H-8), 7.88 (d, 1H, J = 8.4, H-5); ^{13}C NMR (CDCl$_3$) δ 18.68 (C-3), 19.28 (C-11), 19.44 (C-13), 21.80 (C-14), 27.75 (C-1 and C-2), 32.86 (C-12), 46.00 (C-4), 116.28 (C-9a), 117.44 (C-8a), 119.94 (C-5), 123.90 (C-7), 128.39 (C-6), 128.98 (C-8), 145.93 (C-5a), 146.20 (C-9), 160.68 (C-4a). Minor diastereoisomer (33 %): ^{1}H NMR (CDCl$_3$) δ 0.60 (d, 3H, J = 6.7, H-13), 1.05 (d, 3H, J = 7.0, H-14), 1.21 (d, 3H, J = 7.0, H-11), 1.81 (m, 2H, H-2), 1.88 (m, 2H, H-3), 2.93 (m, 2H, H-1 and H-4), 3.08 (o, 1H, J = 6.5, H-12), 7.30 (t, 1H, J = 7.5, H-7), 7.50 (t, 1H, J = 7.6, H-6), 7.68 (d, 1H, J = 8.2, H-8), 7.86 (d, 1H, J = 8.4, H-5); ^{13}C NMR (CDCl$_3$) δ 16.56 (C-3), 16.68 (C-13), 18.54 (C-11), 20.89 (C-14), 27.81 (C-1), 29.01 (C-2), 30.48 (C-12), 46.90 (C-4), 116.86 (C-9a), 117.07 (C-8a), 119.94 (C-5), 123.90 (C-7), 128.39 (C-6), 128.98 (C-8), 145.93 (C-5a), 146.59 (C-9), 160.68 (C-4a).

3.25. *(1*R*)-9-Amino-1-methyl-4-isopropyl-1,2,3,4-tetrahydroacridine (**13b**)*

Yield 15%. Mp 100–102 °C. HRMS (EI) calcd for $C_{17}H_{22}N_2$ 254.17830, found 254.17844.

3.26. *9-(Pyrazol-1-yl)-1,2,3,4-tetrahydroacridines*

A mixture of 9-chloro-3-methyl-1,2,3,4-tetrahydroacridine (**9a**) (0.5 g, 0.0022 mol) and the corresponding pyrazole (1 g, large excess, between 5 and 7 equivalents) was placed in a Pyrex flask inside a mineralization vessel. After the MW irradiation (W and min) the residue was chromatographed over silica gel (CH_2Cl_2/EtOAc 50:50).

3.27. *9-(Pyrazol-1-yl)-3-methyl-1,2,3,4-tetrahydroacridine (**14a**)*

540 W, 1 min 30 s. Yield 35%. Mp 173–174 °C. HRMS (EI) calcd for $C_{17}H_{17}N_3$ 263.14225, found 263.14284. ^{1}H NMR (CDCl$_3$) δ 1.13 (d, 3H, J = 6.5 Hz, H-11), 1.39 (m, 1H, H-2A), 1.90 (m, 1H, H-2B), 2.04 (m, 1H, H-3), 2.66 (m, 2H, H-1), 2.75 (dd, 1H, J = 17.5, 10.9, H-4A), 3.30 (ddd, 1H, J = 17.5, 5.0, 1.7, H-4B), 6.57 (dd, 1H, J = 2.4, 1.9, H-4′), 7.19 (dd, 1H, J = 8.4, 0.7, H-8), 7.40 (ddd, 1H, J = 8.3, 7.0, 1.1, H-7), 7.61 (dd, 1H, J = 2.4, 0.6, H-5′), 7.66 (ddd, 1H, J = 8.0, 6.9, 1.3, H-6), 7.85 (dd, 1H, J = 1.8, 0.6, H-3′), 8.02 (d, 1H, J = 8.4, H-5). ^{13}C NMR (CDCl$_3$) δ 21.80 (C-11), 24.45 (C-1), 29.13 (C-3), 30.48 (C-2), 42.49 (C-4), 106.73 (C-4′), 122.48 (C-8), 124.59 (C-8a), 126.95(C-7), 127.74 (C-9a), 128.58 (C-5), 129.35 (C-6), 131.66 (C-5′), 141.14 (C-3′), 142.50 (C-9), 147.36 (C-5a), 160.18 (C-4a).

3.28. *9-(3 and 5-Methylpyrazol-1-yl)-3-methyl-1,2,3,4-tetrahydroacridine (**15a** and **16a**)*

540 W, 1 min 30 s. Yield 98%. (**15a**) Mp (decompose). HRMS (EI) calcd for $C_{18}H_{19}N_3$ 277.15790, found 277.15809. ^{1}H NMR (CDCl$_3$) δ 1.17 (d, 3H, J = 6.6, H-11), 1.45 (m, 1H, H-2A), 1.94 (m, 1H, H-2B), 2.08 (m, 1H. H-3), 2.43 (m, 1H, H-1A), 2.45 (s, 3H, H-6′), 2.76 (m, 1H, H-1B), 2.78 (dd, 1H, J = 17.4, 10.9, H-4A), 3.32 (ddd, J = 17.5, 4.9, 1.8, H-4B), 6.38 (d, 1H, J = 2.0, H-4′), 7.31 (dd, 1H, J = 8.4, 0.7, H-8), 7.43 (ddd, 1H, J = 8.1, 7.0, 1.0, H-7), 7.53 (d, 1H, J = 2.1, H-5′,), 7.66 (ddd, 1H, J = 8.4, 7.0, 1.4, H-6), 8.05 (d, 1H, J = 8.4, H-5); ^{13}C NMR (CDCl$_3$) δ 13.73 (C-6′), 21.77 (C-11′), 24.46 (C-1), 29.11 (C-3), 30.52 (C-2), 42.49 (C-4), 106.41 (C-4′), 122.65 (C-8), 124.70 (C-8a), 126.78 (C-7), 127.64 (C-9a), 128.52 (C-5), 129.20 (C-6), 132.30 (C-5′), 142.61 (C-9), 147.40 (C-5a), 150.36 (C-3′), 160.11 (C-4a).

3.29. *9-(5-Methylpyrazol-1-yl)-3-methyl-1,2,3,4-tetrahydroacridine (**16a**)*

Mp (decompose). HRMS (EI) calcd for $C_{18}H_{19}N_3$ 277.15790, found 277.15768. ^{1}H NMR (CDCl$_3$) δ 1.18 (d, 3H, J = 6.6, H-11), 1.48 (m, 1H, H-2A), 1.94 (m, 1H, H-2B), 2.02 and 2.03 (s, 3H, H-6′), 2.08 (m, 1H, H-3), 2.43 (m, 1H, H-1A), 2.76 (m, 1H. H-1B), 2.78 (m, 1H, H-4A), 3.34 (ddd, 1H, J = 17.4, 4.9, 1.8, H-4B), 6.33 (m, 1H, H-4′), 7.05 and 7.07 (d, 1H, J = 8.5, H-8), 7.43 (ddd, 1H, J = 8.1, 7.0, 1.0, H-7), 7.67 (ddd, 1H, J = 8.4, 7.0, 1.3, H-6), 7.75 and 7.76 (d, 1H, J = 1.6, H-3′), 8.08 (d, 1H, J = 8.5, H-5); ^{13}C NMR (CDCl$_3$) δ 10.97 and 11.04 (C-6′), 21.70 and 21.77 (C-11), 24.20 and 24.24 (C-1), 29.01 and 29.29 (C-3), 30.31 and 30.38 (C-2), 42.42 (C-4), 105.72 (C-2′), 122.30 (C-8), 125.11 (C-8a), 127.03 (C-7), 128.64 and 128.70 (C-5), 128.86 and 128.99 (C-9a), 129.30 and 129.35 (C-6), 139.95 and 140.41 (C-5′), 140.94 and 141.01 (C-3′), 141.44 and 141.55 (C-9), 147.37 (C-5a), 160.27 (C-4a).

3.30. Theoretical calculations

AM1 calculations were carried out using the MOPAC software incorporated in the CS Chem 3D Pro Version 4.0 package. The absolute shieldings were calculated within the GIAO approximation [23] using DFT/6-31G* optimized geometries [24,25] with the Gaussian 98 package [26]. At this level, TMS absolute shieldings are 32.1842 ppm (^{1}H) and 189.6914 ppm (^{13}C).

Acknowledgements

We thank Dr. Marcel Pierrot (LBS, Marseille) for providing the necessary facilities and helping in solving the structure of compound *cis*-**10b**.

Appendix A. Crystal structure determination

Crystal data and structure refinement for compound *cis*-**10b** are available from one of us (A.K.). The structure has been registered at the Cambridge Crystallographic Data Centre (CCDC 189487).

References

1 (a) G.M. Shutske, F.A. Pierrat, K.J. Kapples, M.L. Cornfeldt, M.R. Szewczak, F.P. Huger, G.M. Bores, V. Haroutunian, K.L. Davis, J. Med. Chem. 32 (1989) 1805–1813; (b) M.F.M. Braga, A.L. Harvey, E.G. Rowan, Br. J. Pharmacol. 102 (1991) 909–915; (c) M. Pomponi, B. Giardina, F. Gatta, M. Marta, Med. Chem. Res. 2 (1992) 306–327; (d) M.T. McKenna, G.R. Proctor, L.C. Young, A.L. Harvey, J. Med. Chem. 40 (1997) 3516–3523; (e) P. Valenti, A. Rampa, A. Bisi, V. Andrisano, V. Cavrini, L. Fin, A. Buriani, P. Giusti, Bioorg. Med. Chem. Lett 7 (1997) 2599–2602; (f) F. Porcelli, M. Delfini, M.R. Del Giudice, Bioorg. Chem. 27 (1999) 197–205; (g) A. Rampa, A. Bisi, F. Belluti, S. Gobbi, P. Valenti, V. Andrisano, V. Cavrini, A. Cavalli, M. Recanatini, Bioorg. Med. Chem. Lett. 8 (2000) 497–506; (h) M. Recanatini, A. Cavalli, F. Belluti, L. Piazzi, A. Rampa, A. Bisi, S. Gobbi, P. Valenti, V. Andrisano, M. Bartolini, V. Cavrini, J. Med. Chem. 43 (2000) 2007–2018; (i) G.R. Proctor, A.L. Harvey, Curr. Med. Chem. 7 (2000) 295–302; (j) W.K. Summers, J. Alzheimer's Dis. 2 (2000) 85–93; (k) P. Camps, E. Gómez, D. Muñoz-Torrero, A. Badía, N.M. Vivas, X. Barril, M. Orozco, F.J. Luque, J. Med. Chem. 44 (2001) 4733–4736.

[2] A. Cañas-Rodríguez, R.G. Cañas, A. Mateo-Bernardo, An. Quím. Ser. C 83 (1987) 24–27.

[3] G.M. Shutske, G.C. Helsey, K.J. Kapples, Chem. Abstr. 123 (1995) 83218 U.S. US 5391553 A (21 Feb 1995).

[4] (a) D.J. Hagan, E. Gimenez-Arnau, C.H. Schwalbe, M.F.G. Stevens, J. Chem. Soc., Perkin Trans. 1 (1997) 2739–2746; (b) D.J. Hagan, D. Chan, C.H. Schwalbe, M.F.G. Stevens, J. Chem. Soc., Perkin Trans. 1 (1998) 915–924; (c) M. Julino, M.F.G. Stevens, J. Chem. Soc., Perkin Trans. 1 (1998) 1677–1684; (d) M. Julino, P.R. Lowe, M.F.G. Stevens, J. Chem. Res., Synop (2000) 74–75; (e) M.J. Ellis, M.F.G. Stevens, J. Chem. Soc., Perkin Trans. 1 (2001) 3174–3179.

[5] M.J. Plater, I. Greig, M.H. Helfrich, S.H. Ralston, J. Chem. Soc., Perkin Trans. 1 (2001) 2553.

[6] I. Cristea, M.M. Popovici, M.T. Mendel, I. Silaghi-Dumitrescu, E. Kozma, Heterocycl. Comm. 5 (1999) 543–548.

[7] H. Tiedke, Chem. Ber. 42 (1909) 621–626.

[8] R.A. Reed, J. Chem. Soc. (1944) 425–426.

[9] A. Albert, The Acridines, second ed, Arnold, London, 1966, pp. 53.

[10] W.H. Perkin, W.G. Sedgwick, J. Chem. Soc. 125 (1924) 2437–2451.

[11] J. Elguero, B. Shimizu, An. Quím. 84C (1988) 176–182.

[12] H.K. Sen, U.P. Basu, J. Indian Chem. Soc. 6 (1929) 309–318.

[13] U.P. Basu, S.T. Das Gupta, J. Indian Chem. Soc. 14 (1937) 468–473.

[14] G.K. Hughes, F.J. Lions, Proc. Roy. Soc. N.S.W. 71 (1938) 458–461.

[15] J. Sotiropoulos, N. El Batouti, A.-M. Lamazouère, J. Heterocycl. Chem. 24 (1987) 907–912.

[16] (a) R. Carrasco, R.F. Pellón, J. Elguero, P. Goya, J.A. Paéz, J. Synth. Commun. 19 (1989) 2077–2080; (b) I. Almena, J.R. Carrillo, P. de la Cruz, A. Díaz-Ortiz, M.J. Gómez-Escalonilla, A. de la Hoz, F. Langa, P. Prieto, A. Sánchez-Migallón, Application of microwave irradiation in heterocyclic chemistry, Targets in Heterocyclic Systems, Ital. Soc. Chem., Roma 2 (1998) 281–308; (c) E. Díez-Barra, A. de la Hoz, A. Sánchez-Migallón, J. Elguero, J. Heterocycl. Chem. 36 (1999) 889–894; (d) A. Esteves-Souza, A. Echevarría, I. Vencato, M.L. Jimeno, J. Elguero, Tetrahedron 57 (2001) 6147–6153.

[17] J.V. Braun, A. Heymons, G. Manz, Ber. Dtsch. Chem. Ges. 64 (1931) 227–235.

[18] E.T. Michalson, S. D'Andrea, J.P. Freeman, J. Szmuszkovicz, Heterocycles 30 (1990) 415–425.

[19] R. Faure, J.P. Galy, L. N'Gadi, J. Barbe, Magn. Reson. Chem 27 (1989) 92–95.

[20] R.M. Claramunt, C. López, M.A. García, M.D. Otero, M.R. Torres, E. Pinilla, S.H. Alarcón, I. Alkorta, J. Elguero, New J. Chem. 25 (2001) 1061–1068.

[21] J.K. Harper, J.C. Facelli, D.H. Barich, G. McGeorge, A.E. Mulgrew, D.M. Grant, J. Am. Chem. Soc. 124 (2002) 10589–10595; A. Novoselsky, R. Glaser, Magn. Reson. Chem. 40 (2002) 723–728.

[22] J. Elguero, C. Marzin, A.R. Katritzky, P. Linda, The Tautomerism of Heterocycles, Academic Press, New York, 1976.

[23] R. Ditchfield, Mol. Phys. 27 (1974) 789–807; F. London, J. Phys. Radium 8 (1937) 397–409.

[24] A.D. Becke, Phys. Rev. A 38 (1988) 3098–3100; A.D. Becke, J. Chem. Phys. 98 (1993) 5648–5652; C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785–789.

[25] W.J. Hehre, R. Ditchfield, J.A. Pople, J. Chem. Phys. 56 (1972) 2257–2261; P.A. Hariharan, J.A. Pople, Theor. Chim. Acta 28 (1973) 213–222.

[26] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B.G. Johnson, W. Chen, M.W. Wong, J.L. Andres, M. Head-Gordon, E.S. Replogle, J.A. Pople, Gaussian 98, Revision A. 6, Gaussian, Inc., Pittsburgh, PA, 1998.