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Divergent base-induced reactivity of cycloalkenyl-1-diazenes

Orazio A. Attanasi [a,*], Stefano Berretta [a], Lucia De Crescentini [a], Gianfranco Favi [a], Paolino Filippone [a], Gianluca Giorgi [b], Fabio Mantellini [a,*]

[a] Istituto di Chimica Organica, Università degli Studi di Urbino 'Carlo Bo', Via I Maggetti 24, 61029 Urbino, Italy
[b] Dipartimento di Chimica Organica, Università degli Studi di Siena, Via Aldo Moro, 53100 Siena, Italy

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ABSTRACT

The different base-promoted regioselectivities of the ring closure processes in the reactions between cycloalkenyl-1-diazenes and β-ketoesters are investigated. Under the appropriate conditions it is possible to turn the synthesis towards cycloalkenyliden-pyrroles or functionalized 3-hydroxy-hydrocinnolines. The aromatization procedure of the heteroring counterpart of the 3-hydroxy-hydrocinnolines is also reported.

1. Introduction

Pyridazines and fused pyridazines are of considerable interest because of their synthetic utility[1] and important pharmacological activities, many of them related to the cardiovascular or to central nervous systems.[2] On the other hand, 1,2-diaza-1,3-dienes (DDs) are versatile precursors in organic synthesis for the preparation of a great number of heterocyclic compounds,[3] exhibiting both diene and dienophile roles in Diels–Alder reactions and acting as Michael acceptors. Usually, DDs participate in inverse electron demand Diels–Alder reactions with electron-rich dienophiles giving rise mainly to different tetrahydropyridazines.[4,5] Alternatively, the pyridazine derivatives were prepared from DDs and β-monosubstituted enamines,[6] or from 4-chloro-DDs and 3-dimethylaminopropenoates.[7] The conjugated addition (Michael-type) of activated methylene compounds **B** to the terminal carbon atom of the azo-ene system **A** to produce α-functionalized hydrazones **C** was also extensively studied (Scheme 1). The following cyclization processes involve one of the hydrazonic nitrogen atoms and appropriate functionalities on the attacking nucleophile.[3] Unlike what has been reported previously by Brodka and Simon,[8] we have obtained pyrrole derivatives **D** or **E** as final products starting from **C′**. The 'strongly activated'5-*exo* cyclization[9] (Scheme 1, path a) involves the sp^2 nitrogen and is promoted by the loss of an acidic hydrogen in α-position to the hydrazonic function. This process is favoured in both electron withdrawing moieties like esters or amides, usually located in positions 1 (EWG^2) and 4 (EWG) of the starting DDs **A**, able to enhance their electrophilic character towards the nucleophiles in the Michael additions and also from the aromaticity of the pyrroles **D**,**E** obtained (Scheme 1, path a).

In order to tentatively promote the 6-*exo* cyclization, we have investigated previously the reactions of 4-substituted cycloalkenyl-1-diazenes (CADs) (R^1, R^2=–$(CH_2)_n$–), which lack the above-mentioned hydrogen, with β-dicarbonyl compounds (Scheme 1, path b).[10] Actually, a different 'weakly activated' 5-*exo* cyclization happens in this latter case by means of the base-mediated loss of the weakly activated hydrogen in α-position to the hydrazone group producing cycloalkenyliden-pyrroles **F**. Instead, starting from hydrazones **C‴** obtained from 4-chloro-DDs (EWG=Cl) the reaction produces pyridazines **H** or **I** through a 6-*exo* cyclization that concerns the sp^3 nitrogen (Scheme 1, path c).[11] The presence of Cl as a leaving group on the C4 of the azo-ene skeleton plays a crucial role in the outcome of the reaction. In fact, the key step resides in the formation of the α, β-unsaturated hydrazones **G** as a result of chloridric acid elimination, avoiding the activation of the sp^2 nitrogen.

With the aim to obtain new fused heterocycles, herein we describe the one pot approach to unknown 3-hydroxy-3,4,5,6,7,8-hexahydrocinnolines through a Michael addition–6-*exo* cyclization sequence starting from the same CADs and β-dicarbonyl compounds by varying the basic conditions.

2. Results and discussion

As previously reported,[10] we have demonstrated that the reaction between CADs[12] and β-dicarbonyl compounds in tetrahydrofuran (THF) at room temperature in the presence of a catalytic amount of sodium methoxide (MeONa) represents a useful and convenient entry to cycloalkenyliden-pyrroles **4a** (Scheme 2, path a).

Testing 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)[13] as base in the reaction between CAD **1a** and methyl acetoacetate **2a**, to our surprise, we observed the formation of the new 3-hydroxy-3,4,5,6,7,8-

* Corresponding authors. E-mail addresses: orazio.attanasi@uniurb.it (O.A. Attanasi), fabio.mantellini@uniurb.it (F. Mantellini).

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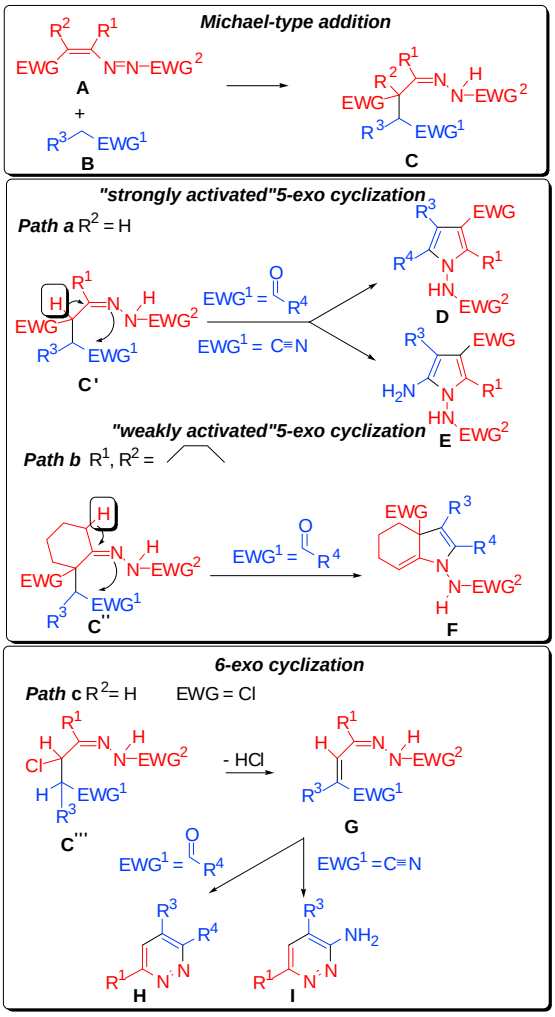
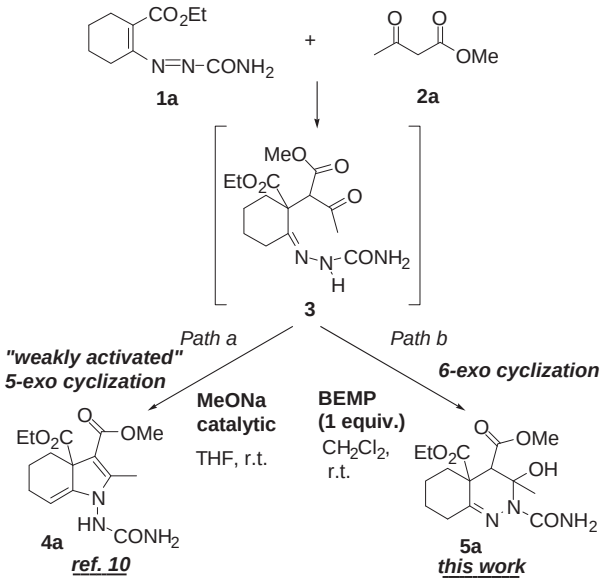


Scheme 1. Possible cycloaddition behaviours in the base-mediated reactions between DDs or CADs and compounds containing activated methylene groups.



Scheme 2. Divergent cyclization processes induced from the different basic conditions in the reaction of CAD **1a** and methyl acetoacetate **2a**.

hexahydrocinnoline **5a** (Scheme 2, path b). This reaction was carried out in dichloromethane, at room temperature, in the presence of a stoichiometric amount of BEMP and required 14 h. This latter synthesis proceeds by means of conjugated addition (Michael-type) of the activated methylene group of **2a** to the terminal carbon atom of the azo-ene system of **1a** producing the hydrazone intermediate **3**. The 6-*exo* cyclization that converts **3** into **5a** involves the nucleophilic attack of the sp^3 hydrazonic nitrogen at the ketonic function of the methyl acetoacetate **2a**. The structure of **5a** was unambiguously confirmed by X-ray analysis (Fig. 1).[14]

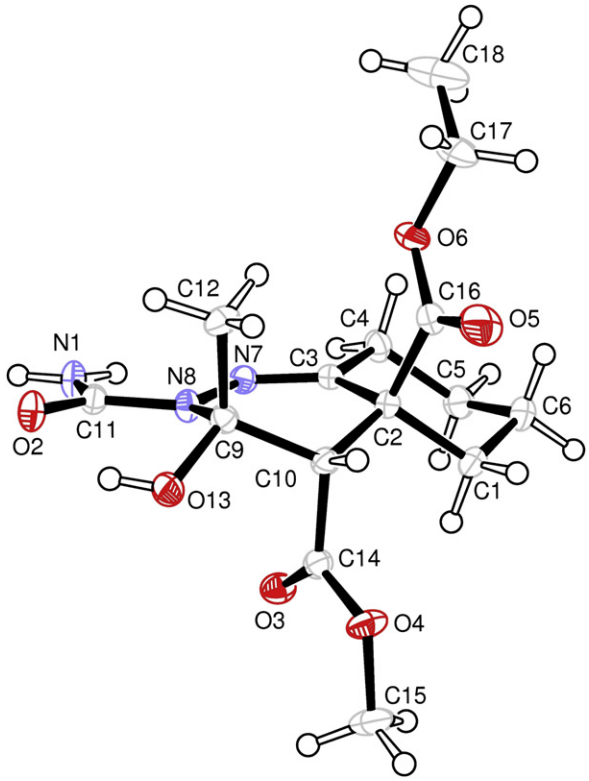


Figure 1. ORTEP drawing of compound **5a**. Ellipsoids enclose 50% probability.

Encouraged by this, other different base–solvent combinations were tested to promote the 6-*exo* cyclization (Table 1). Among the bases screened (used in different amounts), BEMP (0.1 and 1.0 equiv)

Table 1
Screening activity of different basic conditions in the reaction between CAD **1a** and methyl acetoacetate **2a**

Entry	Base	Solvent	Amount (equiv)	Reaction time (h)	Yield[a] (%) **4a**	Yield[a] (%) **5a**
1	BEMP	CH_2Cl_2	0.1	72.0	—	11
2	BEMP	CH_2Cl_2	1.0	14.0	—	26
3	*t*-BuONa	THF	0.1	8.0	24	—
4	*t*-BuONa	THF	1.0	8.0	21	—
5	K_2CO_3	THF	1.0	16.0	—	16
6	K_2CO_3	THF	4.0	16.0	—	27
7	NaH	THF	0.1	0.5	—[b]	—[b]
8	NaH	THF	1.0	0.5	—[b]	—[b]
9	MeONa	THF	0.1	4.0	51	—
10	MeONa	THF	1.0	12.0	—	65
11	DIPEA	THF	1.0	>96	—[c]	—[c]
12	DABCO	THF	1.0	14.0	9	—
13	DBU	THF	0.1	14.0	—[b]	—[b]
14	DBU	THF	1.0	14.0	—[b]	—[b]

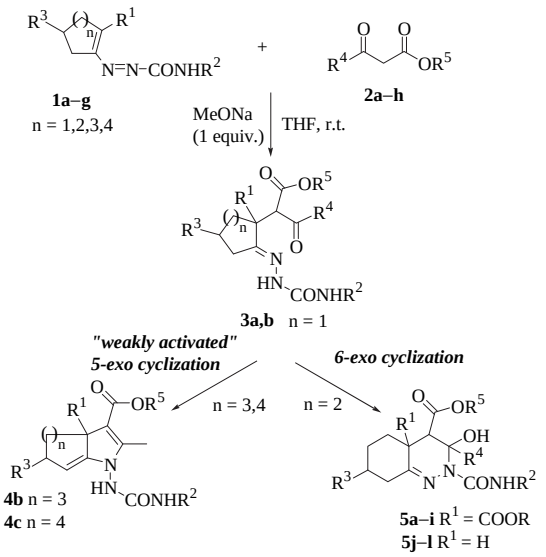
[a] Isolated yields based on starting **1a**.
[b] The reaction gave complicated mixtures.
[c] The reaction didn't occur.

in dichloromethane, potassium carbonate (1.0 and 4.0 equiv) in THF and MeONa (1.0 equiv) in THF all produce 3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline **5a**.

Instead, cycloalkenyliden-pyrrole **4a** was formed using MeONa (0.1 equiv) in THF,[10] sodium *tert*-butylate (*t*-BuONa) (0.1 and 1.0 equiv) in THF and 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.0 equiv) in THF. Sodium hydride (NaH) (0.1 and 1.0 equiv) in THF, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 and 1.0 equiv) in THF yielded a complicated reaction mixture, where neither **4a** nor **5a** was detected by TLC analysis. *N*,*N*-Diisopropylethylamine (DIPEA) (1.0 equiv) in THF was ineffective. In summary, the common and cheap MeONa in stoichiometric amount, in THF, at room temperature gave the best result to promote the 6-*exo* cyclization. It is noteworthy that the amount of the sodium methoxide employed in the reactions changes the regioselectivity of the ring closure process: a catalytic quantity promotes the 'weakly activated' 5-*exo* cyclization,[10] while a stoichiometric amount induces the 6-*exo* one. It is important to note that these cycloadditions proceed with a high regioselectivity. In fact no mixtures of **4a** and **5a** were observed.

The use of these optimized conditions towards 6-*exo* cyclization was extended to the reaction of CADs of different size **1a**–**g** and various alkyl β-ketoesters **2a**–**h** (Scheme 3, Table 2). The 6-*exo* cyclization successfully occurred only starting from cyclohexenyl-1-diazenes **1a**,**c**–**e** (n=2) producing new and functionalized 4,4a-dialkyl-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates **5a**–**i** (R^1=COOR) and alkyl-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j**–**l** (R^1=H) (Scheme 3, Table 2). A further confirmation of the proposed structure derives from X-ray analysis of **5j** (Fig. 2).[14]

The ring size of the starting CADs **1** clearly influences the course of the reactions. In fact, cyclopentenyl-1-diazene **1b** (n=1) provided only the corresponding α-substituted hydrazones **3a**,**b**. As previously reported,[10] all attempts at cyclization of **3a**,**b** failed either by means of heat or under basic or acidic conditions. The cyclohexenyl-1-diazenes **1a**,**c**–**e** (n=2) have the suitable structural requirement that makes possible both ring closure processes (Scheme 3, Table 2). Instead, the reactions of cycloheptenyl-1-diazene (n=3) **1f** and cyclooctenyl-1-diazene **1g** (n=4) with methyl acetoacetate **2a**, in the presence of a stoichiometric amount of MeONa, in THF, at room temperature gave the corresponding cycloalkenyliden-pyrroles **4b**,**c** by means of 'weakly activated' 5-*exo* cyclization and no traces of



Scheme 3. Synthesis of α-substituted cyclopentanone hydrazones **3a**,**b**, cycloalkenyliden-pyrroles **4b**,**c**, 4,4a-dialkyl-2-(aminocarbonyl)-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates **5a**–**i**, and alkyl-2-(aminocarbonyl)-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j**–**l**.

hydrocinnolines were detected.[10] Therefore, the regioselectivity of the cyclization process is a result of a delicate balance that regards both the basic conditions used and the ring size of the starting CAD that influences the ring strain in the final fused bicyclic system. The 'weakly activated' 5-*exo* cyclization produces a carbon–carbon double bond in the cycloalkyl portion of compounds **4** and an increment of this ring size determines a lower ring strain (Scheme 3). So, the 'weakly activated' 5-*exo* cyclization is favoured in the cases of cycloheptenyl- (n=3) **1f** and cyclooctenyl-1-diazenes **1g** (n=4) as starting materials.

Checking the progress of the reactions between 4-substituted cyclohexenyl-1-diazenes **1a**,**c**,**d** (R^1=COOEt, n=2) and **2a**–**g** under the conditions previously described, after the disappearance of the typical red colour of the azo-ene system, the TLC analysis revealed in all cases the presence of two major products. As previously reported,[10] the more polar spots are ascribable to the respective hydrazone intermediates **3**, while the non-polar ones correspond to

Table 2
Isolated yields of α-substituted cyclopentanone hydrazones **3a**,**b**, cycloalkenyliden-pyrroles **4b**,**c**, 4,4a-dialkyl-2-(aminocarbonyl)-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates **5a**–**i**, alkyl-2-(aminocarbonyl)-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j**–**l**, 4-4a-dialkyl-2-(aminocarbonyl)-5,6,7,8-tetrahydrocinnoline-4,4a(2*H*)-dicarboxylates **6a**–**d**, alkyl 2-(aminocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **6e**–**g**, alkyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **7a**–**c** and alkyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylates **8a**–**c**

1	n	R^1	R^2	R^3	2	R^4	R^5	3	Yield[a] (%)	4	Yield[a] (%)	5	Yield[a] (%)	6	Yield[b] (%)	7	Yield[c] (%)	8	Yield[d] (%)
1a	2	CO_2Et	H	H	**2a**	Me	Me					**5a**	65						
1a	2	CO_2Et	H	H	**2b**	Me	$CH_2CH_2OCH_3$					**5b**	63						
1a	2	CO_2Et	H	H	**2c**	Me	Bn					**5c**	56						
1b	1	CO_2Et	H	H	**2a**	Me	Me	**3a**	72										
1b	1	CO_2Et	H	H	**2b**	Me	$CH_2CH_2OCH_3$	**3b**	75										
1c	2	CO_2Et	Ph	H	**2c**	Me	Bn					**5d**	66	**6a**	82				
1c	2	CO_2Et	Ph	H	**2d**	Me	Allyl					**5e**	79	**6b**	80				
1c	2	CO_2Et	Ph	H	**2e**	Me	*t*-Bu					**5f**	61	**6c**	86				
1c	2	CO_2Et	Ph	H	**2f**	Et	Et					**5g**	45	**6d**	76				
1c	2	CO_2Et	Ph	H	**2g**	4-NO_2Ph	Et					**5h**	58						
1d	2	CO_2Et	H	Me	**2a**	Me	Me					**5i**	58						
1e	2	H	Ph	H	**2a**	Me	Me					**5j**	63	**6e**	85	**7a**	83	**8a**	92
1e	2	H	Ph	H	**2d**	Me	Allyl					**5k**	81	**6f**	82	**7b**	68	**8b**	94
1e	2	H	Ph	H	**2h**	Me	Et					**5l**	72	**6g**	78	**7c**	78	**8c**	89
1f	3	CO_2Me	H	H	**2a**	Me	Me			**4b**	68								
1g	4	CO_2Et	H	H	**2a**	Me	Me			**4c**	63								

[a] Isolated yields based on starting **1**.
[b] Isolated yields based on starting **5**.
[c] Isolated yields based on starting **6**.
[d] Isolated yields based on starting **7**.

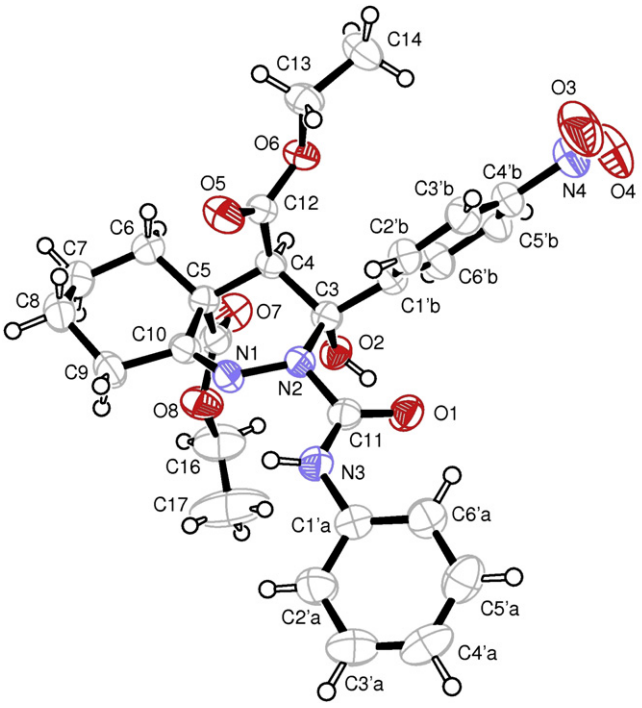
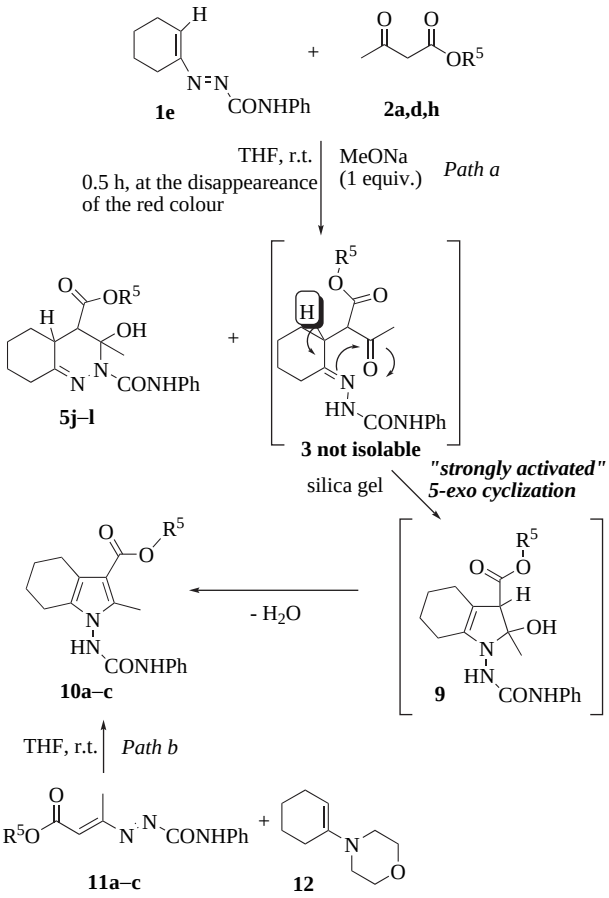


Figure 2. ORTEP drawing of compound **5j**. Ellipsoids enclose 50% probability.

the final products **5a**–**i**. After 14–16 h, the hydrazone intermediates disappeared and only 4,4a-dialkyl-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates **5a**–**i** are present. The attempts to isolate the intermediates **3** failed because the hydrazones spontaneously produce the cycloalkenyliden-pyrroles **4** by means of 'weakly activated' 5-*exo* cyclization during the chromatographic processes, in agreement with our previous results.[10]

Also in the case of reactions between *N*-1-phenyl-2-(1-cyclohexenyl)-1-diazene-1-carboxamide **1e** (R^1=H, *n*=2) and **2a**,**d**,**h**, the TLC check at the disappearance of the red colour shows the presence in all cases of two major products. The less polar ones were identified as alkyl-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylated **5j**–**l**. Instead, during the chromatographic procedures the more polar ones corresponding to the relevant hydrazone adduct intermediates **3** were converted into the related alkyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-carboxylates **10a**–**c** (Scheme 4, path a, Table 3). The presence of one hydrogen originally located in position 4 of the azo-ene system of **1e** permits a 'strong activated' 5-*exo* cyclization that yields the 2-hydroxy-2,3,4,5,6,7-hexahydro-1*H*-indole intermediates **9**. The final loss of a water molecule produces **10a**–**c**. This latter 5-*exo* cyclization is favoured since it furnished aromatic compounds. An alternative route to prepare the same compounds **10a**–**c** starting from DDs **11a**–**c** and 1-morpholinocyclohexene **12** is reported from Sommer[15] and Schultz et al.[16] (Scheme 4, path b, Table 3). The comparison of derivatives **10a**–**c** obtained from the two different synthetic pathways confirms the assigned structure. It is noteworthy that the 'construction' of compounds **10a**–**c** proceeds with different atomic-assembly: choosing, for example, the cyclohexyl portion as reference, it derives from the electrophilic counterpart in the reactions of CAD **1** and β-ketoesters **2** (Scheme 4, path a, Table 3), or from the nucleophilic one starting from DDs **11** and enamine **12** (Scheme 4, path b, Table 3).

Compounds **5** are suitable to produce further interesting derivatives by means of very simple procedures. In the literature, few reports describe the aromatization of the tetrahydropyridazines to



Scheme 4. Synthesis of alkyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-carboxylates **10a**–**c** from CAD **1e** and β-ketoesters **2a**,**d**,**h** or from DDs **11a**–**c** and 1-morpholinocyclohexene **12**.

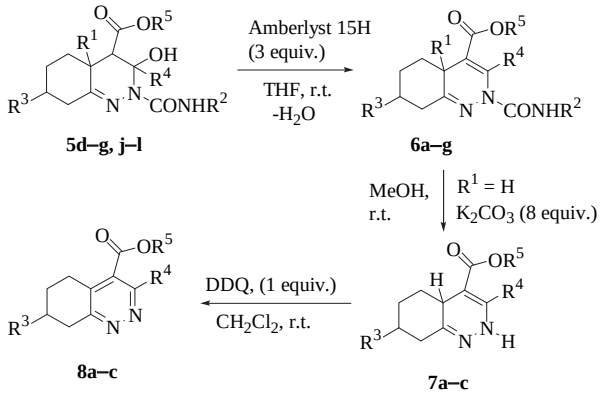
Table 3
Isolated yields of alkyl-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j**–**l** and alkyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-carboxylates **10a**–**c**

5	Yield[a] (%)	**10**	R^5	Yield (%) by **1e**+**2**[a]
5j	10	**10a**	Me	47
5k	8	**10b**	Allyl	52
5l	13	**10c**	Et	41

[a] Isolated yields based on **1e** after chromatographic columns carried out at the disappearance of the starting materials.

the corresponding pyridazines.[5,17] No instances are reported on the conversion of octahydrocinnolines or hexahydrocinnolines into 5,6,7,8-tetrahydrocinnolines. By acidic treatment of 4,4a-dialkyl-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates **5d**–**g** (R^1=COOR) and alkyl-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j**–**l** (R^1=H) with Amberlyst 15H (3 equiv), at room temperature, in THF, the loss of a water molecule occurred producing the novel corresponding 4-4a-dialkyl-(aminocarbonyl)-,5,6,7,8-tetrahydrocinnoline-4,4a(2*H*)-dicarboxylates **6a**–**d** or alkyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **6e**–**g** in high yields (Scheme 5, Table 2). In order to accomplish the aromatization process of the pyridazine portion, potassium carbonate (8 equiv) was added to a solution of the 4a-unsubstituted **6e**–**g** derivatives (R^1=H), in methanol (MeOH), at room temperature. Under these conditions, the hydrolysis of the ureidic moiety occurred and the *N*-unsubstituted derivatives **7a**–**c** were obtained in good yields. The final oxidation of alkyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **7a**–**c** furnished the corresponding alkyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylate

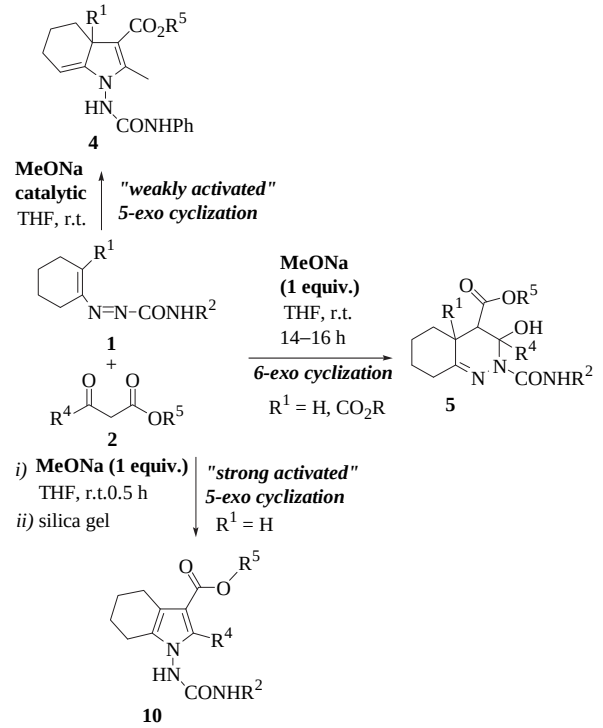
compounds **8a**–**c** by addition of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 1.0 equiv) in dichloromethane, at room temperature (Scheme 5, Table 2).



Scheme 5. Synthesis of 4-4a-dialkyl-2-(aminocarbonyl)-5,6,7,8-tetrahydrocinnoline-4,4a(2*H*)-dicarboxylates **6a**–**d**, alkyl 2-(aminocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **6e**–**g**, alkyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **7a**–**c** and alkyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylates **8a**–**c**.

3. Conclusions

The present investigation evidenced a different base-induced behaviour in the reactions between CADs **1** and β-ketoesters **2**. As a matter of fact, the synthesis indicates that **1** can react with **2** under different basic conditions showing distinct regioselectivity (Scheme 6): (1) 4-substituted CADs (R^1=COOR) in presence of catalytic amount of MeONa produce cycloalkenyliden-pyrroles **4** by means of 'weakly activated' 5-*exo* cyclization; (2) 4-substituted (R^1=COOR) and 4-unsubstituted CADs (R^1=H) with stoichiometric amount of MeONa yield 3-hydroxy-3,4,5,6,7,8-hexahydrocinnolines or 3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnolines **5** through 6-*exo* cyclization; (3) by stopping the reaction of 4-unsubstituted CADs (R^1=H) with stoichiometric amount of MeONa at the disappearance of the starting materials and by chromatographing the crude, 4,5,6,7-tetrahydro-1*H*-indoles **10** were achieved by means of 'strong activated' 5-*exo* cyclization.



Scheme 6. Summary of the different base-induced behaviour in the reactions between CADs **1** and β-ketoesters **2**.

Furthermore, derivatives **5** are powerful intermediates to prepare 5,6,7,8-tetrahydrocinnolines **8**. This synthetic sequence constitutes a new and valid approach in the development of the aromaticity in the heteroring portion. All these reactions proceed under very mild conditions using easily available starting materials and provide interesting new products in good yields without complicated work-up procedures. It is noteworthy that these different hydrocinnolines are not easily available from other methods and they represent new classes of polyheterocycles of interest in organic,[18] biological,[19] medicinal[20] and agricultural chemistry.[21]

4. Experimental section

4.1. General

Methyl, ethyl, 2-methoxyethyl, benzyl, allyl, *tert*-butyl acetoacetates, ethyl propionylacetate, ethyl 4-nitrobenzoylacetate, sodium methoxide, sodium *tert*-butoxide, sodium hydride, potassium carbonate, BEMP, DABCO, DBU, DIPEA, Amberlyst 15H, DDQ, silica gel 35–70 μ were commercial materials and were used without further purification. Solvents were purchased and used without further purification with the exception of THF, which was distilled over sodium hydroxide. Melting points were determined on open capillary tubes. Mass spectra EI were made at an ionizing voltage of 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.32 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (J) values are given in hertz. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$ or DMSO-d_6, as internal standard in a broad band decoupled mode; the multiplicities were obtained using 135° and 90° DEPT experiments to aid in assignment. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad; cy, cycloalkyl; Ar, aromatic. All the NH and NH_2 exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μ for column chromatography. All new compounds shown satisfactory elemental analysis (C±0.35; H±0.30; N±0.30). The nomenclature was generated using ACD/IUPAC Name (version 3.50, 5 Apr. 1998), Advanced Chemistry Development Inc., Toronto, ON (Canada).

4.2. General procedure for the synthesis of α-substituted cyclopentanone hydrazones 3a,b, cycloalkenyliden-pyrroles 4b,c, 4,4a-dialkyl-2-(aminocarbonyl)-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates 5a–i and alkyl-2-(aminocarbonyl)-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates 5j–l

To a magnetically stirred solution of CADs **1a**–**g** (1.0 mmol) and β-ketoesters **2a**–**h** (1.0 mmol) in THF (30 mL) a stoichiometric amount of sodium methoxide was added (1.0 mmol). The reaction mixture was allowed to stand at room temperature and monitored by TLC for 14.0–16.0 h. Starting from cyclopentenyl-1-diazene **1b** and β-ketoesters **2a**,**b**, the reagents disappeared after about 30 min yielding a polar spot. After 14.0 h, the TLC analysis showed no change, and then the reaction solvent was evaporated under reduced pressure and the corresponding cyclopentanone hydrazones **3a**,[10] **b** were obtained by crystallization from ethyl acetate–light petroleum ether (40–60 °C). In the case of 4-carboxylated cyclohexenyl-1-diazenes **1a**, **c**,**d** (R^1=COOEt) or 4-unsubstituted cyclohexenyl-1-diazene **1e** (R^1=H)

with **2a**–**g**, at the disappearance of the typical red colour of the CADs (15–30 min) the TLC check revealed the presence of two major products. After 14.0–16.0 h the more polar spot disappeared. Then, the reaction solvent was evaporated under reduced pressure and the crudes were chromatographed on silica column (elution mixture: 20% ethyl acetate–cyclohexane) obtaining the corresponding 4,4a-dialkyl-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylate **5a**–**i** (R^1=COOEt) and alkyl-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylate (R^1=H) **5j**–**l**. Compounds **5a**–**l** were crystallized from ethyl acetate–light petroleum ether (40–60 °C). Starting from cycloheptenyl-1-diazene **1f** or from cyclooctenyl-1-diazene **1g** and **2a**, at the disappearance of the typical red colour the TLC analysis revealed the presence of two spots. After 4.0–6.0 h, only the less polar one remained. The reaction solvent was evaporated under reduced pressure and the crudes were chromatographed on silica column (elution mixture: 20% ethyl acetate–cyclohexane) obtaining the corresponding cycloalkenyliden-pyrroles **4b**,**c**[10] that were crystallized from diethyl ether–cyclohexane.

*4.2.1. Ethyl 2-[2-(aminocarbonyl)hydrazono]-1-{1-[(2-methoxyethyl)carbonyl]-2-oxopropyl}cyclopentanecarboxylate (**3b**).* White solid; 288 mg (75%); mp 136–138 °C. Found: C, 51.63; H, 6.72. $C_{16}H_{25}N_3O_7$ requires C, 51.74; H, 6.78%. ν_{max} (Nujol) 3365, 3225, 1782, 1742 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.18 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.58–1.65 (m, 1H, cy), 1.95–2.08 (m, 2H, cy), 2.18 (s, 3H, Me), 2.28–2.40 (m, 2H, cy), 2.58–2.71 (m, 1H, cy), 3.36 (s, 3H, OMe), 3.64 (s, 1H, CH), 3.42–3.64 (m, 2H, OCH_2CH_2O), 4.02–4.24 (m, 4H, OCH_2CH_3, OCH_2CH_2O), 5.17 and 6.09 (br s, 2H, NH_2), 7.63 (br s, 1H, NH) ppm; δ_C (100.6 MHz, DMSO-d_6) 14.5 (q), 19.7 (q), 27.3 (t), 28.0 (t), 29.1 (q), 30.1 (t), 58.2 (d), 62.3 (t), 63.6 (t), 64.7 (s), 70.4 (t), 145.3 (s), 154.9 (s), 169.2 (s), 171.4 (s), 201.7 (s) ppm; MS: *m*/*z*=371 [M^+, 8], 340 (2), 325 (38), 297 (15), 268 (80), 254 (36), 223 (13), 195 (100%).

*4.2.2. 4a-Ethyl 4-methyl 2-(aminocarbonyl)-3-hydroxy-3-methyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5a**).* White solid; 222 mg (65%); mp 145–147 °C. Found: C, 52.70; H, 6.76. $C_{15}H_{23}N_3O_6$ requires C, 52.78; H, 6.79%. ν_{max} (Nujol) 3411, 3253, 3189, 1754, 1733, 1679 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.08–1.30 (m, 2H, cy), 1.25 (t, *J*=7.2 Hz, 3H, OCH_2CH_3), 1.31 (s, 3H, Me), 1.63–1.70 (m, 1H, cy), 1.80–1.87 (m, 1H, cy), 2.01–2.08 (m, 1H, cy), 2.54–2.62 (m, 3H, cy), 3.29 and 3.33 (s, 1H, CH), 3.60 (s, 3H, OMe), 4.14–4.25 (m, 2H, OCH_2CH_3), 6.86 and 6.95 (2br s, 2H, NH_2), 7.68 (s, 1H, OH) ppm; δ_C (100.6 MHz, DMSO-d_6) 13.7 (q), 13.8 (q), 21.4 (t), 25.2 (t), 26.2 (q), 32.4 (t), 34.3 (t), 47.6 (d), 51.4 (q), 51.6 (q), 54.3 (s), 62.1 (t), 82.2 (s), 142.2 (s), 159.1 (s), 168.8 (s), 171.9 (s) ppm; MS: *m*/*z*=341 [M^+, 15], 323 (5), 298 (20), 280 (33), 267 (100), 250 (38), 235 (13), 220 (21), 207 (84),193 (47), 151 (100%).

*4.2.3. 4a-Ethyl 4-(2-methoxyethyl) 2-(aminocarbonyl)-3-hydroxy-3-methyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5b**).* White solid; 243 mg (63%); mp 138–140 °C. Found: C, 52.88; H, 7.10. $C_{17}H_{27}N_3O_7$ requires C, 52.98; H, 7.06%. ν_{max} (Nujol) 3425, 3213, 3120, 1768, 1716, 1637 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.35–1.51 (m, 2H, cy), 1.44 (s, 3H, Me), 1.64–1.70 (m, 2H, cy), 1.84–1.90 (m, 1H, cy), 2.17–2.21 (m, 1H, cy), 2.50–2.57 (m, 1H, cy), 2.67–2.76 (m, 1H, cy), 3.33 (s, 3H, OMe), 3.53 (s, 1H, CH), 3.48–3.62 (m, 2H, OCH_2CH_2O), 4.11–4.28 (m, 4H, OCH_2CH_3, OCH_2CH_2O), 5.15 and 6.52 (br s, 2H, NH_2), 7.32 (br s, 1H, OH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.0 (q), 21.7 (t), 25.2 (t), 26.3 (q), 33.0 (t), 34.4 (t), 48.1 (d), 54.3 (s), 58.6 (q), 62.1 (t), 63.5 (t), 70.1 (t), 83.0 (s), 145.3 (s), 159.0 (s), 168.9 (s), 172.0 (s) ppm; MS: *m*/*z*=385 [M^+, 5], 342 (3), 311 (22), 281 (1), 251 (100), 235 (12), 207 (13), 193 (100%).

*4.2.4. 4-Benzyl 4a-ethyl 2-(aminocarbonyl)-3-hydroxy-3-methyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5c**).* White solid; 234 mg (56%); mp 151–153 °C. Found: C, 60.48; H, 6.47. $C_{21}H_{27}N_3O_6$ requires C, 60.42; H, 6.52%. ν_{max} (Nujol) 3487, 3370, 1734, 1676, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15–1.20 (m, 2H, cy), 1.28 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.41 and 1.46 (2s, 3H, Me), 1.58–1.64 (m, 2H, cy), 1.81–1.84 (m, 1H, cy), 2.11–2.14 (m, 1H, cy), 2.49–2.55 (m, 1H, cy), 2.66–2.75 (m, 1H, cy), 3.56 (s, 1H, CH), 4.12–4.26 (m, 2H, OCH_2CH_3), 5.15 and 5.19 (2s, 2H, OCH_2Bn), 6.02 and 6.12 (2br s, 2H, NH_2), 6.57 (br s, 1H, OH), 7.25–7.37 (m, 5H, Ar) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.0 (q), 21.7 (t), 25.3 (t), 26.3 (q), 26.6 (t), 26.8 (t), 33.0 (t), 34.5 (t), 48.3 (d), 54.5 (s), 62.1 (t), 66.5 (t), 83.0 (s), 84.2 (s), 128.1 (d), 128.3 (d), 128.4 (d), 135.5 (s), 145.2 (s), 148.1 (s), 158.9 (s), 159.4 (s), 168.7 (s), 171.9 (s) ppm; MS: *m*/*z*=417 [M^+, 2], 399 (9), 372 (34), 344 (52), 328 (160), 312 (79), 284 (100), 239 (61), 211 (73), 168 (72%).

*4.2.5. 4-Benzyl 4a-ethyl 2-(anilinocarbonyl)-3-hydroxy-3-methyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5d**).* White solid; 325 mg (66%); mp 153–154 °C. Found: C, 65.78; H, 6.26. $C_{27}H_{31}N_3O_6$ requires C, 65.71; H, 6.33%. ν_{max} (Nujol) 3395, 3289, 3143, 1775, 1712, 1689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23–1.33 (m, 3H, OCH_2CH_3), 1.36–1.43 (m, 2H, cy), 1.47 and 1.55 (2s, 3H, Me), 1.61–1.67 (m, 1H, cy), 1.83–1.90 (m, 1H, cy), 2.13–2.20 (m, 1H, cy), 2.53–2.66 (m, 2H, cy), 2.71–2.80 (m, 1H, cy), 3.16 and 3.62 (2s, 1H, CH), 4.13–4.20 (m, 2H, OCH_2CH_3), 5.14–5.24 (m, 2H, OCH_2Bn), 7.05–7.26 (m, 1H, Ar), 7.29–7.47 (m, 10H, Ar, OH), 9.69 and 8.72 (2br s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.3 (q), 14.4 (q), 22.0 (t), 22.9 (t), 25.6 (t), 26.7 (q), 27.0 (t), 27.1 (t), 33.4 (t), 34.8 (t), 48.7 (d), 50.8 (d), 55.0 (s), 57.3 (s), 62.3 (t), 62.5 (t), 67.0 (t), 67.1 (t), 67.2 (t), 83.6 (s), 85.0 (s), 120.1 (d), 120.3 (d), 123.8 (d), 124.0 (d), 128.5 (d), 128.7 (d), 128.8 (d), 129.1 (d), 129.2 (d), 135.8 (s), 137.8 (s), 145.8 (s), 148.6 (s), 155.1 (s), 155.5 (s), 168.4 (s), 169.1 (s), 170.2 (s), 172.2 (s) ppm; MS: *m*/*z*=493 [M^+, 12], 448 (7), 420 (55), 386 (48), 358 (100), 313 (42), 285 (69), 266 (62), 238 (31%).

*4.2.6. 4-Allyl 4a-ethyl 2-(anilinocarbonyl)-3-hydroxy-3-methyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5e**).* White solid; 350 mg (79%); mp 140–142 °C. Found: C, 62.35; H, 6.63. $C_{23}H_{29}N_3O_6$ requires C, 62.29; H, 6.59%. ν_{max} (Nujol) 3384, 1757, 1740, 1716, 1672 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.08–1.30 (m, 2H, cy), 1.25 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.31 (s, 3H, Me), 1.61–1.71 (m, 1H, cy), 1.83–1.94 (m, 1H, cy), 2.23–2.29 (m, 1H, cy), 2.23–2.48 (m, 2H, cy), 2.61–2.73 (m, 1H, cy), 3.54 and 3.59 (2s, 1H, CH), 4.15–4.33 (m, 2H, OCH_2CH_3), 4.55–4.71 (m, 2H, $OCH_2CH{=}CH_2$), 5.22–5.29 (m, 1H, $OCH_2CH{=}CH_2$), 5.37 (d, 1H, *J*=17.2 Hz, $OCH_2CH{=}CH_2$), 5.86–5.98 (d, 1H, *J*=17.2 Hz, $OCH_2CH{=}CH_2$), 7.07 (t, 1H, *J*=7.6 Hz, Ar), 7.21 (br s, 1H, OH), 7.32 (t, 2H, *J*=7.6 Hz, Ar), 7.45 (d, 2H, *J*=8.8 Hz, Ar), 8.70 and 8.73 (2br s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 13.8 (q), 13.9 (q), 21.7 (t), 22.0 (q), 25.3 (t), 25.5 (t), 26.1 (q), 26.3 (q), 26.8 (t), 33.1 (t), 33.2 (t), 34.6 (t), 55.6 (d), 61.9 (t), 62.2 (t), 65.5 (t), 65.6 (t), 82.2 (s), 83.3 (s), 118.5 (d), 119.2 (d), 119.6 (d), 119.8 (d), 120.0 (d), 123.3 (d), 123.4 (d), 128.8 (s), 128.9 (s), 131.2 (d), 131.7 (d), 137.5 (t), 137.8 (t), 145.5 (s), 154.6 (s), 158.8 (s), 168.6 (s), 171.3 (s), 171.9 (s) ppm; MS: *m*/*z*=443 [M^+, 12], 398 (8), 386 (24), 369 (84), 358 (59), 249 (100), 238 (17), 210 (100), 193 (93), 165 (42%).

*4.2.7. 4-tert-Butyl 4a-ethyl 2-(anilinocarbonyl)-3-hydroxy-3-methyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5f**).* White solid; 280 mg (61%); mp 145–147 °C. Found: C, 62.86; H, 7.18. $C_{24}H_{33}N_3O_6$ requires C, 62.73; H, 7.24%. ν_{max} (Nujol) 3378, 1736, 1722, 1688, 1678 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.28 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.31 and 1.33 (2s, 9H, *t*-Bu), 1.47 and 1.53 (2s, 3H, Me), 1.58–1.68 (m, 3H, cy), 1.74–1.83 (m, 1H, cy), 1.82–1.98 (m, 1H, cy), 2.26–2.32 (m, 1H, cy), 2.41–2.47 (m, 1H, cy), 2.68–2.80 (m, 1H, cy), 3.38 and 3.40 (2s, 1H, CH), 4.18–4.32 (m, 2H, OCH_2CH_3), 7,08 (t, 1H, *J*=7.6 Hz, Ar), 7.18 and 7.20 (2s, 1H, OH), 7.30 (t, 2H, *J*=7.6 Hz, Ar), 7.45 (d, 2H, *J*=8.4 Hz, Ar), 8.74 (br s, 1H, NH) ppm; δ_C (100.6 MHz,

$CDCl_3$) 14.0 (q), 21.9 (t), 25.5 (t), 26.6 (q), 26.8 (t), 28.0 (q), 29.6 (t), 33.2 (t), 34.4 (t), 49.1 (d), 54.3 (s), 62.1 (t), 81.7 (s), 83.6 (s), 119.6 (d), 119.9 (d), 123.5 (d), 128.9 (d), 137.6 (s), 145.7 (s), 154.8 (s), 172.2 (s) ppm; MS: m/z=459 [M^+, 8], 414 (13), 386 (62), 358 (100), 313 (70), 285 (72), 266 (18), 237 (100%).

*4.2.8. Diethyl 2-(anilinocarbonyl)-ethyl-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5g**).* White solid; 200 mg (45%); mp 146–148 °C. Found: C, 62.12; H, 6.97. $C_{23}H_{31}N_3O_6$ requires C, 62.01; H, 7.01%. ν_{max} (Nujol) 3405, 3372, 1764, 1717, 1653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.95 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.20–1.36 (m, 7H, 1cy and $2CH_2CH_3$), 1.40–1.60 (m, 3H, cy), 1.66–1.79 (m, 2H, CH_2CH_3), 1.91–1.97 (m, 1H, cy), 2.20–2.30 (m, 1H, cy), 2.60–2.71 (m, 1H, cy), 2.74–2.90 (m, 1H, cy), 3.62 (s, 1H, CH), 4.10–4.30 (m, 4H, $2OCH_2CH_3$), 7.07 (t, 1H, J=7.6 Hz, Ar), 7.18 (s, 1H, OH), 7.31 (t, 2H, J=8.0 Hz, Ar), 7.45 (d, 2H, J=8.8 Hz, Ar), 8.78 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 7.40 (q), 8.19 (q), 14.0 (q), 21.9 (t), 25.5 (t), 30.4 (t), 33.1 (t), 34.8 (t), 48.2 (d), 50.1 (s), 60.8 (t), 61.0 (t), 62.3 (t), 62.4 (t), 85.1 (s), 86.3 (s), 119.8 (d), 123.4 (d), 128.8 (d), 137.6 (s), 145.5 (s), 155.0 (s), 169.1 (s), 172.1 (s) ppm; MS: m/z=445 [M^+, 13], 399 (25), 372 (100), 327 (74), 299 (62), 280 (12), 252 (45), 207 (24%).

*4.2.9. Diethyl 2-(anilinocarbonyl)-3-hydroxy-3-(4-nitrophenyl)-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5h**).* White solid; 312 mg (58%); mp 163–165 °C. Found: C, 60.31; H, 5.64. $C_{27}H_{30}N_4O_8$ requires C, 60.22; H, 5.61%. ν_{max} (Nujol) 3247, 3149, 3094, 1734, 1692, 1607 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.24 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.29 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.30–1.38 (m, 1H, cy), 1.63–1.72 (m, 1H, cy), 1.85–1.93 (m, 1H, cy), 2.03–2.11 (m, 1H, cy), 2.67–2.75 (m, 1H, cy), 2.80–2.86 (m, 1H, cy), 3.27 (s, 1H, CH), 3.62–3.80 (m, 2H, cy), 4.08–4.27 (m, 4H, $2OCH_2CH_3$), 6.98 (t, 1H, J=7.2 Hz, Ar), 7.15 (s, 1H, OH), 7.24 (t, 2H, J=7.2 Hz, Ar), 7.56 (d, 2H, J=7.2 Hz, Ar), 7.76–7.85 (m, 1H, Ar), 8.06–8.13 (m, 1H, Ar), 8.17–8.25 (m, 1H, Ar), 8.24–8.35 (m, 1H, Ar), 9.51 and 9.64 (2s, 1H, NH) ppm; δ_C (100.6 MHz, DMSO-d_6) 13.5 (q), 13.9 (q), 14.1 (q), 21.4 (t), 21.8 (t), 24.7 (t), 25.1 (t), 32.4 (t), 33.7 (t), 58.6 (s), 60.5 (t), 61.3 (t), 81.4 (s), 119.5 (d), 120.2 (d), 122.2 (d), 123.6 (d), 125.8 (s), 126.8 (d), 128.4 (d), 138.8 (s), 146.0 (s), 146.3 (s), 150.8 (s), 152.3 (s), 167.9 (s), 171.0 (s) ppm; MS: m/z=538 [M^+, 18], 493 (51), 465 (77), 420 (84), 392 (100), 373 (64), 344 (17), 300 (10), 272 (93%).

*4.2.10. 4a-Ethyl 4-methyl 2-(aminocarbonyl)-3-hydroxy-3,7-dimethyl-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2H)-dicarboxylate (**5i**).* White solid; 206 mg (58%); mp 143–145 °C. Found: C, 54.14; H, 7.11. $C_{16}H_{25}N_3O_6$ requires C, 54.07; H, 7.09%. ν_{max} (Nujol) 3323, 1781, 1712, 1695, 1655 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 0.86 (d, 3H, J=6.8 Hz, CH_3CH), 1.25 (t, 3H, 7.2 Hz, OCH_2CH_3), 1.31 (s, 3H, CH_3C), 1.43–1.57 (m, 3H, cy), 1.84–1.88 (m, 1H, cy), 2.12–2.20 (m, 1H, cy), 2.23–2.31 (m, 1H, cy), 2.81 and 2.84 (2d, 1H, J=6.0 and 5.8 Hz, $CHCH_3$), 3.30 and 3.32 (s, 1H, CH), 3.59 and 3.60 (s, 3H, OCH_3), 4.13–4.27 (m, 2H, OCH_2CH_3), 6.87 and 6.92 (2br s, 2H, NH_2), 7.67 (s, 1H, OH) ppm; δ_C (100.6 MHz, DMSO-d_6) 13.7 (q), 13.8 (q), 17.6 (t), 26.1 (t), 26.3(q), 27.0 (t), 27.6 (t), 27.7 (t), 28.2 (d), 47.4 (d), 51.4 (q), 54.6 (s), 62.2 (t), 82.3 (s), 142.3 (s), 159.1 (s), 169.0 (s), 171.9 (s) ppm; MS: m/z=335 [M^+, 8], 324 (27), 310 (56), 269 (100), 282 (62), 251 (50), 238 (82), 223 (100), 179 (84%).

*4.2.11. Methyl 2-(anilinocarbonyl)-3-hydroxy-3-methyl-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylate (**5j**).* White solid; 217 mg (63%); mp 135–137 °C. Found: C, 62.66; H, 6.75. $C_{18}H_{23}N_3O_4$ requires C, 62.59; H, 6.71%. ν_{max} (Nujol) 3470, 3369, 1739, 1668, 1592 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.10–1.22 (m, 1H, cy), 1.38–1.50 (m, 2H, cy), 1.56 (s, 3H, Me), 1.85–2.00 (m, 3H, cy), 2.22 (dt, 1H, J=13.2, 5.2 Hz, CH_2CHCH), 2.58 (br s, 1H, OH), 2.59–2.66 (m, 2H, cy), 2.86 (d, 1H, J=12.0 Hz, CH_2CHCH), 3.79 (s, 3H, OMe), 7.08 (t, 1H, J=7.6 Hz, Ar), 7.32 (t, 2H, J=7.6 Hz, Ar), 7.44 (d, 2H, J=7.6 Hz, Ar), 8.67 (br s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 20.4 (q), 24.4 (t), 26.1(t), 31.6 (t), 34.2 (t), 37.7 (d), 52.4 (q), 54.2 (d), 85.4 (s), 120.0 (d), 123.6 (d), 128.9 (d), 137.4 (s), 151.8 (s), 155.8 (s), 171.6 (s) ppm; MS: m/z=345 (M^+, 40), 327 (7), 254 (14), 253 (100), 235 (24), 208 (37), 193 (40), 179 (64), 166 (34), 149 (100), 136 (32%).

*4.2.12. Allyl 2-(anilinocarbonyl)-3-hydroxy-3-methyl-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylate (**5k**).* White solid; 301 mg (81%); mp 134–136 °C. Found: C, 64.59; H, 6.84. $C_{20}H_{25}N_3O_4$ requires C, 64.67; H, 6.78%. ν_{max} (Nujol) 3447, 3368, 1741, 1710, 1688, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.14–1.29 (m, 2H, cy), 1.41–1.52 (m, 2H, cy), 1.57 (s, 3H, Me), 1.84–2.00 (m, 3H, cy), 2.22 (dt, 1H, J=14.0, 5.2 Hz, CH_2CHCH), 2.58 (br s, 1H, OH), 2.59–2.66 (m, 1H, cy), 2.88 (d, 1H, J=12.0 Hz, CH_2CHCH), 4.68–4.74 (m, 2H, $OCH_2CH{=}CH_2$), 5.26 (dd, 1H, J=10.8, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.40 (dd, 1H, J=17.2, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.88–6.00 (m, 1H, $OCH_2CH{=}CH_2$), 7.07 (t, 1H, J=7.6 Hz, Ar), 7.29 (t, 2H, J=7.6 Hz, Ar), 7.45 (d, 2H, J=7.2 Hz, Ar), 8.67 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 20.4 (q), 24.4 (t), 26.1 (t), 31.5 (t), 34.3 (t), 37.3 (d), 54.3 (d), 65.7 (t), 85.4 (s), 118.4 (t), 119.9 (d), 123.6 (d), 128.8 (d), 131.7 (d), 137.5 (s), 151.8 (s), 155.7 (s), 170.8 (s) ppm; MS: m/z=371[M^+, 15], 353 (8), 279 (52), 261 (10), 234 (43), 205 (87), 193 (100), 177 (22), 165 (28), 149 (100), 136 (17), 119 (71%).

*4.2.13. Ethyl 2-(anilinocarbonyl)-3-hydroxy-3-methyl-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylate (**5l**).* White solid; 258 mg (72%); mp 139–141 °C. Found: C, 63.54; H, 7.04. $C_{19}H_{25}N_3O_4$ requires C, 63.49; H, 7.01%. ν_{max} (Nujol) 3421, 3355, 1732, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.14–1.23 (m, 1H, cy), 1.32 (t, 3H, J=6.4 Hz, OCH_2CH_3), 1.41–1.51 (m, 2H, cy), 1.57 (s, 3H, Me), 1.84–2.00 (m, 3H, cy), 2.22 (dt, 1H, J=13.6, 5.2 Hz, CH_2CHCH), 2.58 (br s, 1H, OH), 2.61–2.66 (m, 2H, cy), 2.83 (d, 1H, J=12.0 Hz, CH_2CHCH), 4.21–4.32 (m, 2H, OCH_2CH_3), 7.08 (t, 1H, J=7.2 Hz, Ar), 7.34 (t, 2H, J=7.6 Hz, Ar), 7.44 (d, 2H, J=8.4 Hz, Ar), 8.66 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.0 (q), 20.4 (q), 24.5 (t), 26.1 (t), 31.5 (t), 34.3 (t), 37.8 (d), 54.4 (d), 61.3 (t), 85.5 (s), 120.0 (d), 123.6 (d), 128.9 (d), 137.5 (s), 151.8 (s), 155.8 (s), 171.1 (s) ppm; MS: m/z=359 [M^+, 13], 341 (6), 267 (35), 249 (10), 222 (28), 193 (100), 180 (32), 149 (74%).

4.3. General procedure for the synthesis of 4-4a-dialkyl-2-(aminocarbonyl)-5,6,7,8-tetrahydrocinnoline-4,4a(2*H*)-dicarboxylates 6a–d or alkyl 2-(aminocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates 6e–g, of alkyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates 7a–c and alkyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylate compounds 8a–c

4,4a-Dialkyl-2-(aminocarbonyl)-3-hydroxy-3,4,5,6,7,8-hexahydrocinnoline-4-4a(2*H*)-dicarboxylates **5d–g** and alkyl-2-(aminocarbonyl)-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j–l** were dissolved in THF (20 mL) and 3 equiv of Amberlyst 15 was added. The reaction mixture was magnetically stirred gently for 4.0–5.0 h at room temperature until the disappearance of the starting materials (monitored by TLC). 4-4a-Dialkyl-2-(aminocarbonyl)-5,6,7,8-tetrahydrocinnoline-4,4a(2*H*)-dicarboxylates **6a–d** were obtained from **5d–g** and alkyl 2-(aminocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **6e–g** were obtained from **5j–l**. Products **6a–g** were purified by column chromatography on silica gel (elution mixture: 15% ethyl acetate–cyclohexane) and by subsequent crystallization from diethyl ether–cyclohexane. In order to prepare alkyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylates **7a–c**, to a solution of **6e–g** in MeOH (20 mL) potassium carbonate (8 equiv) was added. The reaction mixture was allowed to stand at room temperature under magnetic stirring until the disappearance of the starting **6e–g** (4.0–6.0 h, monitored by TLC). The reaction solvent was then evaporated under reduced pressure, the crudes were

chromatographed on silica column (elution mixture: 15% ethyl acetate–cyclohexane) and products **7a**–**c** were collected pure by crystallization from ethyl acetate–cyclohexane. Alkyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylates **8a**–**c** were obtained by addition of DDQ (1 equiv) to a solution of **7a**–**c** in dichloromethane. The mixture was magnetically stirred at room temperature until the disappearance of the starting material (0.5–3.0 h, monitored by TLC). Then, the reaction solvent was evaporated under reduced pressure and the crudes were chromatographed on silica column (elution mixture: 10% ethyl acetate–cyclohexane) obtaining the desired compounds **8a**–**c** that were crystallized from diethyl ether–light petroleum ether (40–60 °C).

*4.3.1. 4-Benzyl 4a-ethyl 2-(anilinocarbonyl)-3-methyl-5,6,7,8-tetrahydrocinnoline-4,4a(2H)-dicarboxylate (**6a**).* White solid; 388 mg (82%); mp 92–94 °C. Found: C, 68.28; H, 6.17. $C_{27}H_{29}N_3O_5$ requires C, 68.19; H, 6.15%. ν_{max} (Nujol) 3373, 1741, 1713, 1697, 1684 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.47–1.67 (m, 2H, cy), 1.71–1.85 (m, 2H, cy), 1.91–1.98 (m, 1H, cy), 2.23–2.35 (m, 2H, cy), 2.47 (s, 3H, Me), 2.49–2.60 (m, 1H, cy), 4.07–4.20 (m, 2H, OCH_2CH_3), 5.14–5.26 (m, 2H, OCH_2Bn), 7.09 (t, 1H, J=7.6 Hz, Ar), 7.30–7.40 (m, 7H, Ar), 7.50 (d, 2H, J=7.6 Hz, Ar), 8.92 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 13.9 (q), 18.3 (q), 22.4 (t), 25.7 (t), 33.3 (t), 34.6 (t), 47.0 (s), 61.7 (t), 66.8 (t), 109.3 (s), 119.7 (s), 123.6 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.9 (d), 135.2 (d), 137.5 (s), 137.7 (s), 150.6 (s), 151.4 (s), 166.4 (s), 169.9 (s) ppm; MS: m/z=475 [M^+, 1], 402 (6), 283 (100), 192 (69), 148 (18), 119 (38%).

*4.3.2. 4-Allyl 4a-ethyl 2-(anilinocarbonyl)-3-methyl-5,6,7,8-tetrahydrocinnoline-4,4a(2H)-dicarboxylate (**6b**).* White solid; 340 mg (80%); mp 87–89 °C. Found: C, 64.81; H, 6.34. $C_{23}H_{27}N_3O_5$ requires C, 64.93; H, 6.40%. ν_{max} (Nujol) 3381, 1735, 1717, 1709, 1703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.51–1.66 (m, 3H, cy), 1.74–1.86 (m, 2H, cy), 1.91–1.98 (m, 1H, cy), 2.25–2.34 (m, 1H, cy), 2.49 (s, 3H, Me), 2.52–2.58 (m, 1H, cy), 4.14–4.25 (m, 2H, OCH_2CH_3), 4.60–4.70 (m, 2H, $OCH_2CH{=}CH_2$), 5.26 (dt, 1H, J_2=10.4 Hz, J_3=1.2 Hz, $OCH_2CH{=}CH_2$), 5.36 (dt, 1H, J_2=17.2 Hz, J_3=1.2 Hz, $OCH_2CH{=}CH_2$), 5.88–5.97 (m, 1H, $OCH_2CH{=}CH_2$), 7.07 (t, 1H, J=7.6 Hz, Ar), 7.29 (t, 2H, J=7.6 Hz, Ar), 7.48 (d, 2H, J=8.8 Hz, Ar), 8.90 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.2 (q), 18.4 (q), 22.7 (t), 26.0 (t), 33.6 (t), 34.9 (t), 47.3 (s), 62.0 (t), 65.8 (t), 109.7 (s), 119.1 (t), 120.0 (d), 123.9 (d), 129.2 (d), 131.9 (d), 137.8 (s), 138.1 (s), 150.9 (s), 151.8 (s),166.5 (s), 170.2 (s) ppm; MS: m/z=425 [M^+, 1], 352 (4), 249 (3), 233 (100), 192 (14), 175 (5), 148 (8%).

*4.3.3. 4-tert-Butyl 4a-ethyl 2-(anilinocarbonyl)-3-methyl-5,6,7,8-tetrahydrocinnoline-4,4a(2H)-dicarboxylate (**6c**).* White solid; 379 mg (86%); mp 74–77 °C. Found: C, 65.18; H, 7.13. $C_{24}H_{31}N_3O_5$ requires C, 65.29; H, 7.08%. ν_{max} (Nujol) 3294, 1776, 1737, 1682, 1637 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.50 (s, 9H, *t*-Bu), 1.55–1.69 (m, 3H, cy), 1.73–1.84 (m, 2H, cy), 1.90–2.01(m, 1H, cy), 2.22–2.31 (m, 1H, cy), 2.46 (s, 3H, Me), 2.50–2.60 (m, 1H, cy), 4.17–4.26 (m, 2H, OCH_2CH_3), 7.10 (t, 1H, J=7.6 Hz, Ar), 7.31 (t, 2H, J=7.6 Hz, Ar), 7.50 (d, 2H, J=8.8 Hz, Ar), 8.90 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.1 (q), 17.9 (q), 22.5 (t), 25.7 (t), 28.0 (q), 33.5 (t), 34.3 (t), 47.0 (s), 61.7 (t), 82.0 (s), 111.2 (s), 119.7 (s), 123.5 (d), 128.9 (d), 135.2 (d), 137.9 (s), 150.8 (s), 151.3 (s), 165.7 (s), 169.8 (s) ppm; MS: m/z=441 (M^+, 1), 368 (11), 295 (11), 249 (100), 193 (100), 175 (20), 148 (25), 119 (29%).

*4.3.4. Diethyl 2-(anilinocarbonyl)-3-ethyl-5,6,7,8-tetrahydrocinnoline-4,4a(2H)-dicarboxylate (**6d**).* White solid; 324 mg (76%); mp 81–83 °C. Found: C, 64.59; H, 6.87. $C_{23}H_{29}N_3O_5$ requires C, 64.62; H, 6.84%. ν_{max} (Nujol) 3301, 1753, 1737, 1697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.20 (t, 3H, J=7.2 Hz, CH_2CH_3), 1.24–1.32 (m, 6H, $2OCH_2CH_3$), 1.55–1.63 (m, 3H, cy), 1.77–1.81 (m, 2H, cy), 1.90–1.96 (m, 1H, cy), 2.28–2.35 (m, 1H, cy), 249–2.66 (m, 3H, cy CH_2CH_3), 4.13–4.29 (m, 4H, $2OCH_2CH_3$), 7.09 (t, 1H, J=7.6 Hz, Ar), 7.33 (t, 2H, J=8.0 Hz, Ar), 7.51 (d, 2H, J=7.6 Hz, Ar), 8.93 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 13.7 (q), 14.0 (q), 22.4 (t), 23.6 (q), 25.4 (t), 29.7 (t), 33.2 (t), 34.0 (t), 46.7 (s), 60.9 (t), 61.7 (t), 109.8 (s), 119.8 (d), 123.6 (d), 128.9 (d), 137.9 (s), 142.0 (s), 150.3 (s), 151.5 (s),166.4 (s), 169.8 (s) ppm; MS: m/z=427 [M^+,1], 354 (2), 263 (2), 235 (100), 207 (23), 179 (7), 149 (9), 119 (21%).

*4.3.5. Methyl 2-(anilinocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylate (**6e**).* White solid; 278 mg (85%); mp 79–81 °C. Found: C, 66.13; H, 6.44. $C_{18}H_{21}N_3O_3$ requires C, 66.04; H, 6.47%. ν_{max} (Nujol) 3368, 1728, 1693, 1614 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.39–1.49 (m, 1H, cy), 1.57–1.70 (m, 2H, cy), 1.84–1.90 (m, 1H, cy), 1.93–2.00 (m, 1H, cy), 2.08–2.12 (m, 1H, cy), 2.19–2.27 (m, 1H, cy), 2.48–2.54 (m, 1H, cy), 2.59 (s, 3H, Me), 3.45 (dd, 1H, J=12.0, 4.0 Hz, CH), 3.76 (s, 3H, OMe), 7.08 (t, 1H, J=7.2 Hz, Ar), 7.33 (t, 2H, J=7.6 Hz, Ar), 7.52 (d, 2H, J=7.6 Hz, Ar), 8.92 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 19.1 (q), 26.0 (t), 29.4 (t), 34.9 (t), 35.2 (t), 37.8 (d), 51.5 (s), 106.2 (s), 119.6 (d), 123.5 (d), 128.9 (d), 137.9 (s), 143.3 (s), 151.1 (s), 159.1 (s), 167.9 (s) ppm; MS: m/z=327 [M^+, 8], 208 (57), 193 (67), 179 (100), 166 (62), 149 (33), 119 (47%).

*4.3.6. Allyl 2-(anilinocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylate (**6f**).* White solid; 289 mg (82%); mp 84–86 °C. Found: C, 68.09; H, 6.62. $C_{20}H_{23}N_3O_3$ requires C, 67.97; H, 6.56%. ν_{max} (Nujol) 3384, 1746, 1674, 1630 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.41–1.49 (m, 1H, cy), 1.60–1.69 (m, 2H, cy), 1.83–1.89 (m, 1H, cy), 1.96–2.03 (m, 1H, cy), 2.07–2.14 (m, 1H, cy), 2.18–2.24 (m, 1H, cy), 2.46–2.53 (m, 1H, cy), 2.60 (s, 3H, Me), 3.47 (dd, 1H, J=12.0, 4.0 Hz, CH), 4.65–4.69 (m, 2H, $OCH_2CH{=}CH_2$), 5.25 (dd, 1H, J=12.0, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.34 (dd, 1H, J=17.2, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.91–6.01 (m, 1H, $OCH_2CH{=}CH_2$), 7.07 (t, 1H, J=7.6 Hz, Ar), 7.32 (t, 2H, J=7.6 Hz, Ar), 7.51 (d, 2H, J=8.8 Hz, Ar), 8.93 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 19.0 (q), 25.9 (t), 29.3 (t), 34.8 (t), 35.0 (t), 37.8 (d), 64.9 (t), 106.0 (s), 117.9 (t), 117.9 (d), 123.4 (d), 128.8 (d), 132.2 (d), 137.8 (s), 143.5 (s), 151.0 (s), 159.0 (s), 166.8 (s) ppm; MS: m/z=353 [M^+, 13], 296 (62), 268 (100), 191 (62), 176 (83), 149 (39%).

*4.3.7. Ethyl 2-(anilinocarbonyl)-3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylate (**6g**).* White solid; 266 mg (78%); mp 76–78 °C. Found: C, 66.79; H, 6.82. $C_{19}H_{23}N_3O_3$ requires C, 66.84; H, 6.79%. ν_{max} (Nujol) 3392, 1763, 1713, 1645 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.42–1.49 (m, 1H, cy), 1.60–1.70 (m, 2H, cy), 1.84–1.92 (m, 1H, cy), 1.95–2.03 (m, 1H, cy), 2.06–2.13 (m, 1H, cy), 2.17–2.27 (m, 1H, cy), 2.44–2.56 (m, 1H, cy), 2.59 (s, 3H, Me), 3.45 (dd, 1H, J=12.0, 4.0 Hz, CH), 4.17–4.28 (m, 2H, OCH_2CH_3), 7.08 (t, 1H, J=7.2 Hz, Ar), 7.33 (t, 2H, J=7.6 Hz, Ar), 7.52 (d, 2H, J=7.6 Hz, Ar), 8.91 (s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.3 (q), 19.9 (q), 26.0 (t), 29.3 (t), 34.8 (t), 35.1 (t), 37.8 (d), 60.3 (t), 106.6 (s), 119.6 (d), 123.5 (d), 128.9 (d), 138.0 (s), 142.8 (s), 151.1 (s), 158.9 (s), 167.4 (s) ppm; MS: m/z=341 [M^+, 34], 296 (73), 268 (100), 191 (43), 176 (100), 149 (15%).

*4.3.8. Methyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylate (**7a**).* White solid; 173 mg (83%); mp 125–127 °C. Found: C, 63.53; H, 7.70. $C_{11}H_{16}N_2O_2$ requires C, 63.44; H, 7.74%. ν_{max} (Nujol) 3307, 1706, 1684 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32–1.43 (m, 1H, cy), 1.46–1.57 (m, 2H, cy), 1.70–1.78 (m, 1H, cy), 1.88–2.02 (m, 3H, cy), 2.07 (s, 3H, Me), 2.19–2.25 (m, 1H, cy), 3.30 (dd, 1H, J=12.0, 4.0 Hz, CH), 3.61 (s, 3H, OMe), 7.35 (br s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 17.7 (q), 26.2 (t), 29.2 (t), 35.2 (t), 35.6 (t), 36.5 (d), 50.4 (q), 91.7 (s), 145.5 (s), 156.9 (s), 168.3 (s) ppm; MS: m/z=208 [M^+, 37], 206 (80), 193 (26), 179 (100), 149 (90), 125 (60), 111 (100%).

*4.3.9. Allyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylate (**7b**).* White solid; 159 mg (68%); mp 118–120 °C. Found: C, 66.72;

H, 7.68. $C_{13}H_{18}N_2O_2$ requires C, 66.64; H, 7.74%. ν_{max} (Nujol) 3328, 1712, 1671 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.39–1.48 (m, 1H, cy), 1.52–1.63 (m, 2H, cy), 1.76–1.83 (m, 1H, cy), 1.92–2.08 (m, 3H, cy), 2.12 (s, 3H, Me), 2.22–2.31 (m, 1H, cy), 3.31–3.40 (m, 1H, CH), 4.53–4.60 (m, 2H, $OCH_2CH{=}CH_2$), 5.17 (dd, 1H, J=12.0, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.28 (dd, 1H, J=17.2, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.86–5.97 (m, 1H, $OCH_2CH{=}CH_2$), 6.94 (br s,1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 17.9 (q), 26.4 (t), 29.3 (t), 35.3 (t), 35.7 (t), 36.7 (d), 63.9 (t), 92.2 (s), 117.0 (t), 133.1 (d), 145.6 (s), 157.2 (s), 167.5 (s) ppm; MS: m/z=234 [M^+, 59], 193 (100), 149 (38), 111 (100%).

*4.3.10. Ethyl 3-methyl-2,4a,5,6,7,8-hexahydrocinnoline-4-carboxylate (**7c**).* White solid; 173 mg (78%); mp 124–126 °C. Found: C, 64.92; H, 8.20. $C_{12}H_{18}N_2O_2$ requires C, 64.84; H, 8.16%. ν_{max} (Nujol) 3363, 1758, 1654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.28 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.31–1.44 (m, 1H, cy), 1.50–1.59 (m, 2H, cy), 1.61–1.69 (m, 1H, cy), 1.77–2.06 (m, 3H, cy), 2.09 (s, 3H, Me), 2.17–2.30 (m, 1H, cy), 3.36 (dd, 1H, J=11.6, 4.0 Hz, CH), 4.04–4.19 (m, 2H, OCH_2CH_3), 6.64 (br s, 1H, NH) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.5 (q), 17.9 (q), 26.4 (t), 29.4 (t), 35.3 (t), 35.7 (t), 36.7 (d), 59.1 (t), 92.8 (s), 145.0 (s), 157.1 (s), 167.9(s) ppm; MS: m/z=222 [M^+, 62], 193 (9), 177 (100), 149 (84), 125 (62), 111 (100%).

*4.3.11. Methyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylate (**8a**).* White solid; 190 mg (92%); mp 74–76 °C. Found: C, 64.14; H, 6.91. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84%. ν_{max} (Nujol) 1736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.75–1.83 (m, 2H, cy), 1.85–1.92 (m, 2H, cy), 2.60 (s, 3H, Me), 2.72 (t, 2H, J=6.4 Hz, cy), 3.11 (t, 2H, J=6.4 Hz, cy), 3.92 (s, 3H, OMe) ppm; δ_C (100.6 MHz, $CDCl_3$) 20.1 (q), 21.5 (t), 21.9 (t), 25.5 (t), 30.0 (t), 52.5 (q), 130.8 (s), 133.1 (s), 152.8 (s), 158.6 (s), 166.9 (s) ppm; MS: m/z=206 [M^+, 100], 175 (9), 163 (4), 150 (10), 117 (27%).

*4.3.12. Allyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylate (**8b**).* White solid; 218 mg (94%); mp 82–85 °C. Found: C, 67.29; H, 7.00. $C_{13}H_{16}N_2O_2$ requires C, 67.22; H, 6.94%. ν_{max} (Nujol) 1762 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.75–1.82 (m, 2H, cy), 1.87–1.92 (m, 2H, cy), 2.61 (s, 3H, Me), 2.74 (t, 2H, J=6.4 Hz, cy), 3.12 (t, 2H, J=6.4 Hz, cy), 4.80–4.84 (m, 2H, $OCH_2CH{=}CH_2$), 5.33 (d, 1H, J=9.6 Hz, $OCH_2CH{=}CH_2$), 5.41 (d, 1H, J=17.2 Hz, $OCH_2CH{=}CH_2$), 5.91–5.99 (m, 1H, $OCH_2CH{=}CH_2$) ppm; δ_C (100.6 MHz, $CDCl_3$) 20.0 (q), 21.5 (t), 21.8 (t), 25.4 (t), 29.9 (t), 66.5 (t), 120.3 (t), 131.8 (s), 133.6 (d), 152.9 (s), 158.7 (s), 166.0 (s) ppm; MS: m/z=232 [M^+, 100], 191 (5), 175 (6), 147 (11%).

*4.3.13. Ethyl 3-methyl-5,6,7,8-tetrahydrocinnoline-4-carboxylate (**8c**).* White solid; 196 mg (89%); mp 89–91 °C. Found: C, 65.35; H, 7.32. $C_{12}H_{16}N_2O_2$ requires C, 65.43; H, 7.38%. ν_{max} (Nujol) 1763 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.41 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.79–1.85 (m, 2H, cy), 1.91–1.96 (m, 2H, cy), 2.65 (s, 3H, Me), 2.77 (t, 2H, J=6.4 Hz, cy), 3.15 (t, 2H, J=6.4 Hz, cy), 4.44 (q, 2H, J=7.2 Hz, OCH_2CH_3) ppm; δ_C (100.6 MHz, $CDCl_3$) 13.6 (q), 20.3 (q), 21.4 (t), 21.9 (t), 25.6 (t), 30.2 (t), 62.4 (t), 130.5 (s), 132.7 (s), 152.6 (s), 158.9 (s), 167.3 (s) ppm; MS: m/z=220 [M^+, 100], 175 (18), 163 (3%).

4.4. General procedure for the synthesis of alkyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-carboxylates 10a–c

To a magnetically stirred solution of CAD **1e** (1.0 mmol) and β-ketoesters **2a**,**d**,**h** (1.0 mmol) in THF (30 mL) stoichiometric amount of sodium methoxide was added (1.0 mmol). The reaction mixture was allowed to stand at room temperature until the disappearance of the typical red colour of the starting CAD **1e** (0.5 h). The TLC analysis revealed the presence of two main products. Then, the reaction solvent was evaporated under reduced pressure and the crude was chromatographed on silica column (elution mixture: 20% ethyl acetate–cyclohexane) obtaining the unchanged less polar products that were identified as alkyl-3-hydroxy-2,3,4,4a,5,6,7,8-octahydrocinnoline-4-carboxylates **5j**–**l**. Instead, during the chromatographic process the more polar derivatives were converted into a different products that were identified as alkyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-carboxylates **10a**–**c**. Compounds **10a**–**c** were crystallized from ethyl acetate–cyclohexane.

*4.4.1. Methyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxylate (**10a**).* White solid; 154 mg (47%); mp 216–218 °C. Found: C, 66.10; H, 6.49. $C_{18}H_{21}N_3O_6$ requires C, 66.04; H, 6.47%. ν_{max} (Nujol) 3279, 1705, 1648, 1600, 1574 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.61–1.72 (m, 4H, cy), 2.13–2.25 (m, 1H, cy), 2.32 (s, 3H, Me), 2.36–2.47 (m, 1H, cy), 2.48–2.61 (m, 2H, cy), 3.68 (s, 3H, OMe), 6.98 (t, 1H, J=7.2 Hz, Ar), 7.28 (t, 2H, J=7.2 Hz, Ar), 7.45 (d, 2H, J=7.6 Hz, Ar), 9.22 (br s, 1H, NH), 9.26 (s, 1H, NH) ppm; δ_C (100.6 MHz, DMSO-d_6) 10.5 (q), 20.2 (t), 22.2 (t), 23.0 (t), 23.1 (t), 50.2 (q), 106.8 (s), 115.0 (s), 118.8 (d), 122.3 (s), 128.3 (d), 128.7 (d), 135.7 (s), 139.3 (s), 154.1 (s), 165.5 (s) ppm; MS: m/z=327 (M^+, 22), 192 (100), 175 (3), 160 (16), 132 (11%).

*4.4.2. Allyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxylate (**10b**).* White solid; 184 mg (52%); mp 222–224 °C. Found: C, 68.04; H, 6.51. $C_{20}H_{23}N_3O_3$ requires C, 67.97; H, 6.56%. ν_{max} (Nujol) 3316, 1747, 1664 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.28–1.41 (m, 2H, cy), 1.53–1.79 (m, 4H, cy), 2.28 (s, 3H, Me), 2.42–2.53 (m, 1H, cy), 2.64–2.73 (m, 1H, cy), 4.62–4.74 (m, 2H, $OCH_2CH{=}CH_2$), 5.21 (dd, 1H, J=12.0, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.36 (dd, 1H, J=17.2, 1.6 Hz, $OCH_2CH{=}CH_2$), 5.86–5.94 (m, 1H, $OCH_2CH{=}CH_2$) 7.10 (t, 1H, J=7.6 Hz, Ar), 7.34 (t, 2H, J=7.6 Hz, Ar), 7.57 (d, 2H, J=8.8 Hz, Ar), 7.90 (s, 1H, NH), 7.97 (s, 1H, NH) ppm; δ_C (100.6 MHz, DMSO-d_6) 14.4 (q), 20.2 (t), 22.3 (t), 22.9 (t), 23.2 (t), 65.7 (t), 107.3 (s), 114.8 (s), 118.4 (t), 119.9 (d), 123.6 (d), 124.0 (s), 128.8 (d), 131.7 (d), 135.7 (s), 137.5 (s), 154.2 (s), 166.1 (s) ppm; MS: m/z=353 (M^+, 30), 296 (13), 268 (100), 261 (6), 233 (17), 176 (64), 148 (53%).

*4.4.3. Ethyl 1-[(anilinocarbonyl)amino]-2-methyl-4,5,6,7-tetrahydro-1H-indole-3-carboxylate (**10c**).* White solid; 140 mg (41%); mp 212–214 °C. Found: C, 66.78; H, 6.82. $C_{19}H_{23}N_3O_3$ requires C, 66.84; H, 6.79%. IR (Nujol): ν_{max} 3247, 1713, 1673 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 1.34 (t, 3H, J=6.8 Hz, OCH_2CH_3), 1.70–1.84 (m, 4H, cy), 2.38–2.48 (m, 2H, cy), 2.46 (s, 3H, Me), 2.62–2.68 (m, 2H, cy), 4.26 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.55 (br s, 1H, NH), 7.05–7.11 (m, 2H, Ar), 7.21–7.28 (m, 3H, Ar), 7.81 (s, 1H, NH) ppm; δ_C (100.6 MHz, DMSO-d_6) 10.5 (q), 14.4 (q), 20.6 (t), 22.4 (t), 23.1 (t), 23.3 (t), 59.4 (t), 108.7 (s), 118.0 (s), 120.6 (d), 124.5 (s), 128.1 (d), 129.0 (d), 135.7 (s), 136.8 (s), 155.0 (s), 165.8 (s) ppm; MS: m/z=341 (M^+, 16), 206 (100), 189 (6), 174 (41%).

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References and notes

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14. *X-ray crystallography*. Single crystals of **5a** and **5h** were submitted to X-ray data collections. A Bruker-Nonius FR591 rotating anode (for **5a**) and a Siemens P4 four-circle (for **5h**) diffractometers with graphite monochromated Mo Kα radiation (λ=0.71073 Å) were used for data collections at 120(2) and 293(2) K, respectively. The structures were solved by direct methods implemented in the SHELXS-97 program.[22] The refinements were carried out by full-matrix anisotropic least-squares on F^2 for all reflections for non-H atoms by using the SHELXL-97 program.[23] Both compounds crystallize in the triclinic crystal system, *P*-1 space group, with one molecule that constitutes the asymmetric unit. CCDC-761530 and CCDC-761531 contain the supplementary crystallographic data for compounds **5h** and **5a**, respectively, described in this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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