Novel Cyclic Enaminone Esters and N-Heterocycles by Divergent Chemical Behavior through Amine-Mediated Reactions

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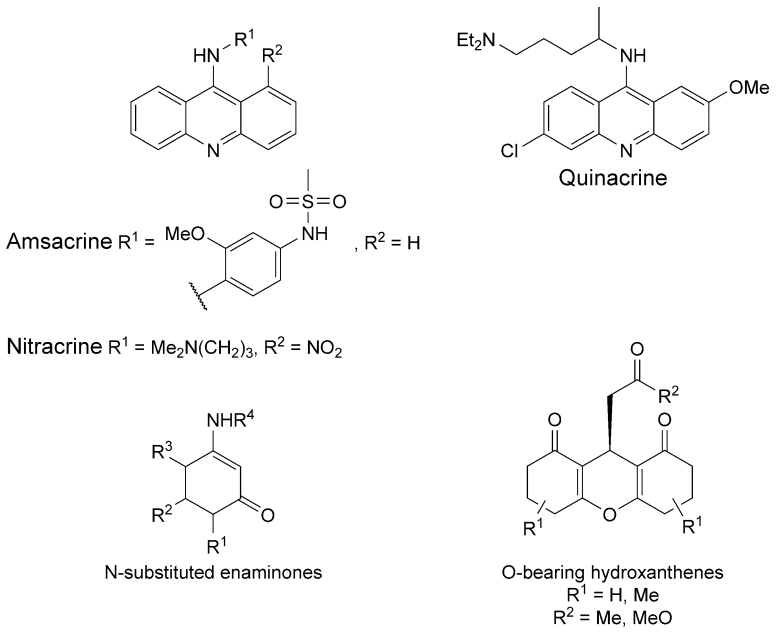
New acridinones and enaminone esters were synthesized by microwave-assisted tandem-*Michael–Michael* addition and cyclization from cyclohexane-1,3-diones. The reaction mechanism for both open and closed structures, and the presence of intramolecular twelve-membered rings derived from NH and OH H-bonds of enaminone esters are discussed.

Introduction. – Drugs, such as amsacrine and nitracrine, both containing an acridine ring, have been used for cancer treatment and also considered as models for the development of new derivatives. The anticancer properties of both structures are attributed to their ability to insert into the DNA, disrupting cellular processes through inhibition of topoisomerase II [1][2].



Acridines and quinolines are also privileged motifs in drug discovery in the field of neurodegenerative and protozoan diseases. As analogs of huperzine and tacrine, 5-amino-5,6,7,8-tetrahydroquinolinones have been synthesized and evaluated for their ability to inhibit cholinesterases, providing effective treatment of *Alzheimer* and myasthenia gravis [3][4].

The 9-aminoacridine unit is also found in quinacrine [5], one of the first known structures used as antimalarial agent. This structure has inspired many scientists to design, synthesize, and evaluate a variety of related compounds [6–8].

In general, acridines are derived from multicomponent reactions of the *Hantzsch* type, *via* conjugate addition between dimedones, amines, and a *Knoevenagel* product [9–12].

Related N-substituted enaminones are also structures of pharmaceutical interest as motifs of 1,4-dihydropyridines or pyran-1,3-diones with antitumor, anticancer, fungicidal, antimalarial, and bactericidal properties [13][14]. In particular, enaminones without substitution at the C-atom of the CH_2(2,2′) groups have been prepared and described since 1971, along with mono enaminone esters that were synthesized and evaluated for their anticonvulsant activities [15].

Exploring new synthetic strategies that contribute to structural diversity in molecules with biological activity, we have synthesized tricyclic ketals based on natural terpenes, such as quassinoids, alkenes from phenylbutyraldehydes [16][17], and more recently O-bearing hydroxanthenes, in solution and solid phase [18–20]. Currently, we have developed a method aimed at discovering new structures for both representative compounds, 1,8-dioxoacridines **3**–**5** and enaminone esters **6**–**10**, as shown in *Scheme 1*.

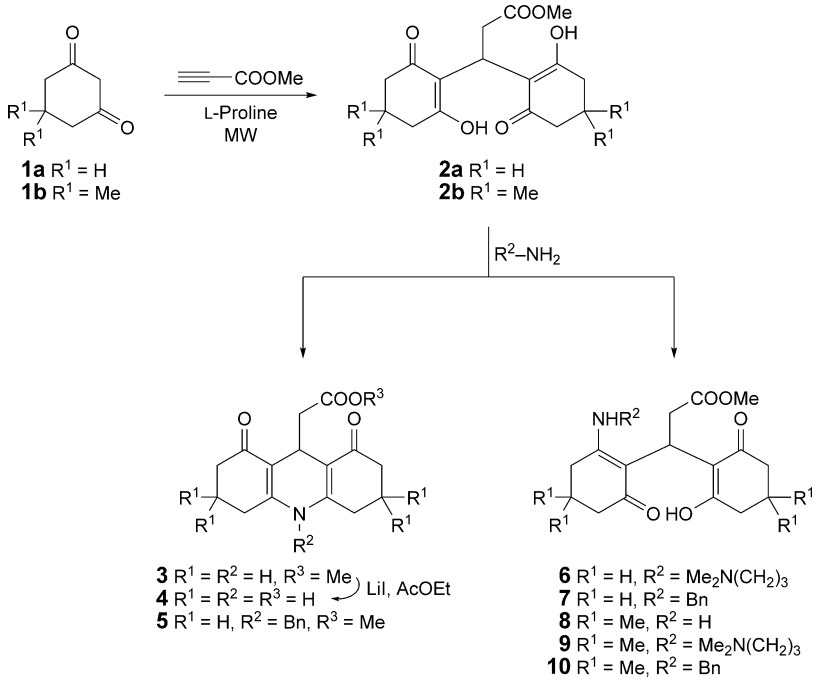
Results and Discussion. – In this work, we developed tandem-*Michael* additions using cyclohexane-1,3-diones **1a** and **1b** with HC≡CCOOMe under L-proline catalysis to give **2a** and **2b** with assistance of microwave heating, which reduced reaction times from 13 d to 15 min at 80° in EtOH. It also increased product yield (88–91%) when compared with the procedure using magnetic stirring at room temperature. Once formation of **2a** and **2b** was achieved, we planned the cyclization reaction with $AcONH_4$, $BnNH_2$, or *N*,*N*-dimethylpropane-1,3-diamine as source to introduce the N-atom required for the heterocycle unit (*Scheme 1*).

Incorporation of the NH group with $AcONH_4$ to bis-dione **2a** (R = H) in a CF_3CH_2OH solution at 70° during 5.5 h gave **3** in 65% yield. When the same reaction was carried out with **2b** under magnetic stirring or sonication, a mixture of non-identified products was observed. This outcome shows the difference in dione reactivity, which translates into the absence or failure in the formation of the corresponding enaminone.

To fulfill the requirements for the synthetic transformations of the ester/acid series, we chose to convert crude ester **3** to the parent acid **4** (66% yield) under LiI/AcOEt conditions.

The more reactive compound **2a** could be converted into the *N*-benzyl tricycle **5** in 70% yield, using $BnNH_2$ by boiling of a solution of **2a** in benzene for 14 h. On the contrary, the reaction of the more substituted compound **2b** with $AcONH_4$, *N*,*N*-dimethylpropane-1,3-diamine, or $BnNH_2$ in AcOH or benzene under reflux (*ca.* 13 h)

Scheme 1. *Synthesis of N-Heterocycles* **3**–**5** *and Enaminone Esters* **6**–**10**



did not provide the acridine core. Likewise, other less substituted diones, such as 5-methyl and 4,4-dimethyl cyclohexanediones, showed low reactivities under different reaction conditions leading to mixtures of products in very low yields.

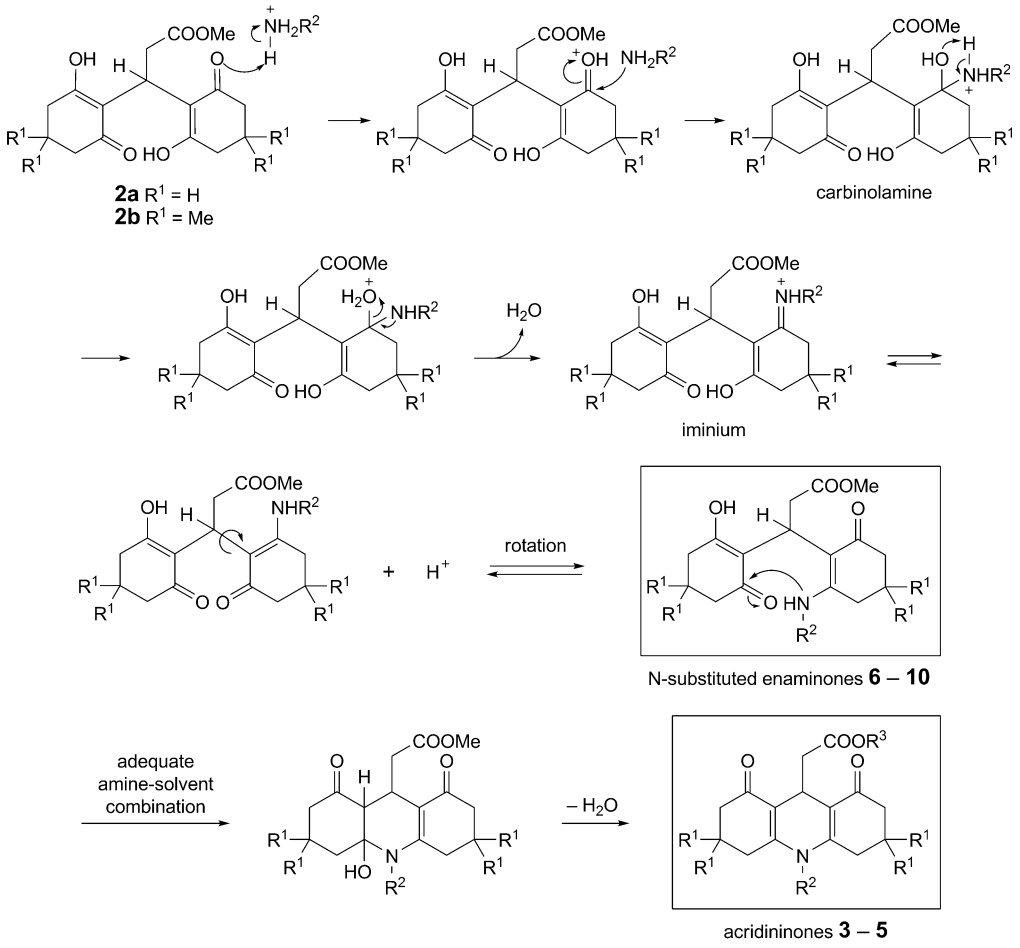
Dimedone **1b** showed greater reactivity with $BnNH_2$ when compared to cyclohexane-1,3-dione **1a** under microwave irradiation. In fact, **2b** produced enaminone **8**, although with an associated reaction of *N*-debenzylation in acidic media [21].

When the reactions of **2a** and **2b** with *N*,*N*-dimethylpropane-1,3-diamine were performed in benzene under reflux for 8–13 h, only the new corresponding products **6** and **9** were obtained after careful chromatography and in moderate yields (52 and 61%, resp.).

Compound **7** was achieved by the reaction of **2a** with $BnNH_2$ in EtOH at 45° for 8 h as colorless pure oil after two rounds of chromatographic purification in moderate yield (63%). However, according to the difference in reactivity between **1a** and **1b**, microwave assistance was necessary to obtain **10** (73% yield).

The different behavior of **2a** and **2b** in the amine reactions under diverse reaction conditions can be explained regarding the keto-enol and iminium-enaminone tautomerisms involved in the reaction. Therefore, we propose a reaction mechanism which accounts for both structures with a first step that includes the nucleophilic addition of the amine (or ammonia) to one of the C=O groups in **2** to form the corresponding carbinolamine (*Scheme 2*). Subsequently, this carbinolamine undergoes dehydration to give an intermediate implicated in an iminium-enaminone tautomeric equilibrium. In a second step, if a 180° rotation occurs, such enaminones (vinylogous

Scheme 2. *Reaction Mechanism Underlying the Formation of Both Structures: Heterocycles* **3**–**5** *and Enaminones* **6**–**10**



amides) produce an intramolecular nucleophilic attack at the C=O group of the other dione motif. Then, the subsequent hemiaminal eliminates the OH group by dehydration to give decahydrodioxoacridines **3**–**5**. Likewise, when the open structure is stabilized by H-bonding, it does neither render heterocycles, nor a lactam generated by intramolecular reaction between amino and ester groups [22a]. A related reaction has been described by *Dubas-Sluyter et al.* between ketones and HC≡CCOOH to give 1,8-dioxoperhydroacridines [22b]. The NMR spectra of **3**–**5** were similar and showed a simple pattern of nucleus signals which were related by the plane of symmetry within these molecules. Products **6**–**10**, that were derived from **2** in the presence of L-proline, were chiral compounds but obtained as mixtures and they showed no net optical activities. The NMR spectra of **6**–**10** sharing chemical shift patterns were more complex than those of precursors **2**. These spectra showed the H-atoms of the CH_2

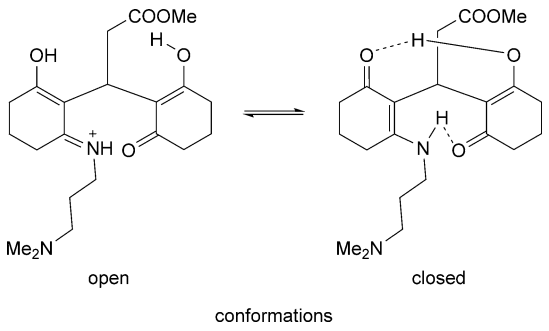
group in the ester moiety as diastereotopic. For example, the ^{1}H-NMR spectrum of **7** showed signals at δ(H) 14.69 and 9.57 for H-atoms implicated in H-bond interactions. Aromatic H-atoms appeared in the range between δ(H) 7.31 and 7.17, while the CH_2 group of the BnNH moiety was detected at 4.46. The CH_2 group in the ester moiety exhibited a set of two *doublets* of *doublet*s at δ(H) 3.24 and 2.90, each one integrating for one H-atom. A value of $J = 16.1$ was due to coupling between H_α-atoms while $J =$ 6.9 corresponded to coupling with the neighboring H-atom. In the ^{13}C-NMR spectrum of **7**, an increase in the number of signals, in respect to **2**, provided evidence that there was no symmetry in the molecule. In the IR spectra of **6**–**10**, the bands of C=O and NH groups were characteristic of H-bonded systems (see the *Exper. Part*).

The GC/MS of **6** showed two peaks: the major one (t_R 34.76 min) with *m*/*z* 58 corresponding to the fragment of the cationic radical $Me_2HN^+CH_2^{\cdot}$ derived from the iminium species. The smallest peak that appeared at t_R 34.27 min corresponded to the fragment ions of the enaminone species: *m*/*z* 94, 108, and 164. This analysis of **6** confirmed the presence of two species in solution, while GC/MS analysis of **7** showed a single peak at t_R 70.25 min, corresponding to the fragmentation of the enaminone species (*m*/*z* 108) towards the cationic $BnNH_3^+$.

These compounds also show prototropic tautomerism, which is an important process in many organic transformations. The keto-enol and enamine-imine tautomerisms are the subject of research given their importance not only in organic chemistry, but also in biological processes. In some cases, the tautomerism to a stable enamine is rare and requires stabilization by extensive delocalization of electrons, forming more complex structures, or H-bonds [23]. In this sense, ^{1}H-NMR spectra of **6**–**10** showed two signals displaced at low field, δ(H) 9 for NH and another one at 15 for OH, both involved in H-bonds. Therefore, in comparison with drug-like organic molecules that interact with their biomolecular targets, we postulate the presence of two H-bonds, with both donors present in the molecule, that generate a temporary ring system, a situation that often occurs in a thermodynamic equilibrium between closed and open conformations (*Scheme 3*) [24].

The molecular geometries of **7** and **10** were calculated using the MMplus molecular mechanics method and then optimized with the semiempirical AM1 method at the UHF level, using HyperChem package software, version 7.01. The *Figure* shows the

Scheme 3. *Proposed Structure with Internal H-Bonds: Thermodynamic Equilibrium between Open and Closed Conformations*



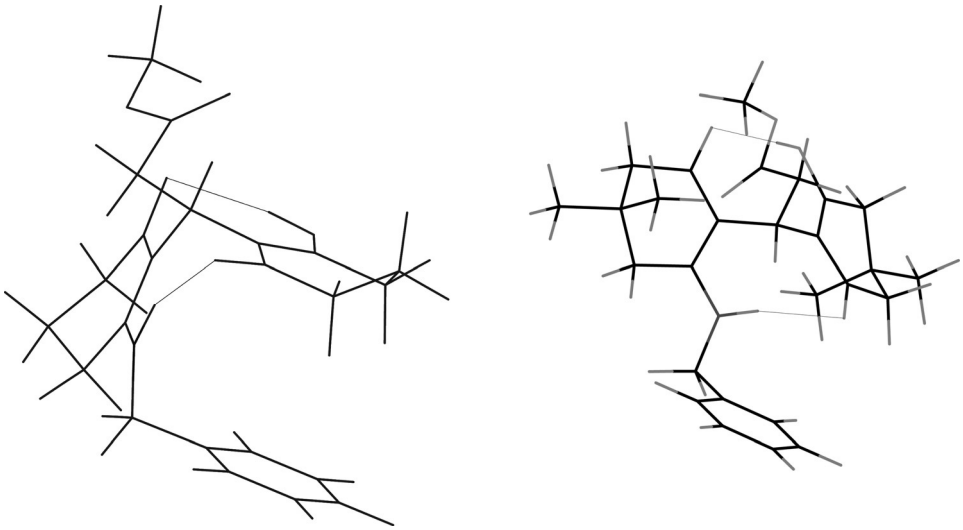


Figure. *Schematic depiction of H-bond interactions of* **7** (left) *and* **10** (right) *involving two moieties*

minimum energy conformations of **7** and **10** (15.75725 and 17.09042 kcal mol^{-1}, resp.), whose cyclic moieties are held together by two H-bonds. The N–H ··· O=C distances are 2.01 and 2.09 Å with bond angles of *ca.* 156.7° for **7** and 162.5° for **10**, while the O–H ··· O=C distances are 2.19 and 1.97 Å, with bond angles of 168.4 and 159.7°, respectively.

These interactions may be a dominant factor governing the stability of these vinylogous amides, which do not display the expected reactivities to proceed with the cyclization to the heterocycle of acridine [24].

The distinct conformations adopted by the product of **2a** with $BnNH_2$ in polar and non-polar environments illustrate the formation of **7** and **5**, respectively.

Structures comparable to **6**–**10** were found as intermediates in the synthesis of 9,10-diarylacridine-1,8-diones in ionic liquid [10]. Moreover, these compounds could be of interest for their very selective interactions bearing a resemblance to the pairing of bases among portions of purines and pyrimidines in nucleic acids in which the H-atom of the NH group participates in interactions leading to an arrangement of two eight-membered cycles [25][26]. Intermolecular interactions involving H-bonds are also responsible for catalysis and molecular recognition [27].

Conclusions. – In conclusion, the robustness of the tandem-*Michael–Michael*-cyclization strategy previously developed for syntheses of xanthenediones from cyclohexane-1,3-diones is now applied to the synthesis of N-heterocycles, decahydro-1,8-dioxoacridine-9-acetic acid (**4**), and its methyl esters **3** and **5**, and methyl 3-(2-amino-6-oxocyclohex-1-en-1-yl)-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)propanoates **6**–**10**. Thus, we were able to construct two different types of compounds of prospective biological interest through a single key precursor that follows different routes according to amine/solvent combination and reaction conditions.

Compounds **3**–**5** are appealing structures since they allow subsequent functionalization of their side chain and rings. Compounds **6**–**10** structurally display an attractive array of H-bonds whose multiple cyclic H-atom transfer involves NH and OH donors, leading to H-bonding arrays of heterocyclic units.

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Experimental Part

General. All reagents and solvents were used directly as purchased or purified according to standard procedures. All reactions involving air- or moisture-sensitive materials, were carried out under N_2. Microwave heating was performed in a *CEM Discover®* System using septum-sealed 10-ml vials for high-pressure reaction conditions under stirring and IR-monitored temp. control. Flash column chromatography (FC): silica gel (SiO_2; 300–400 mesh); under slight N_2 pressure with increasing gradients of solvent mixtures. IR Spectra: *Shimadzu Prestige-21* spectrophotometer; liquid films in NaCl; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance-300 MHz* NMR spectrometer (300.13 and 75.4 MHz, resp.); in $CDCl_3$; δ in ppm rel. to solvent as internal standard, *J* in Hz. GC/MS: *Shimadzu QP-2010 plus* spectrometer. HR-ESI-MS: *LC-QTOf Bruker MicroTOF QII*; in *m*/*z*.

Molecular geometries of **7** and **10** were calculated using the MMplus molecular mechanics method and then optimized with the semiempirical AM1 method at UHF level using HyperChem version 7.01 software. Enthalpies of formation were obtained by AM1 from single point calculations on the optimized geometries.

Procedure for the Microwave-Assisted Tandem-Michael–Michael *Reaction* [28]. 1,3-Dione (1 mmol) dissolved in anh. EtOH (3 ml) was added to an oven-dried 10-ml pressure-rated reaction vial equipped with a stirring bar. Then, HC≡CCOOMe (0.088 ml, 1.1 mmol) and L-proline (18 mg, 6 mol-%) were added. The resulting soln. was stirred at 80° in the microwave reactor until complete conversion of the dione. After 15 min, the solvent was removed under reduced pressure, and the crude product was dissolved in AcOEt (3 ml). Finally, NH_4Cl (1 ml) was added. The aq. phase was extracted with AcOEt (2×3 ml), and the org. phase was dried (Na_2SO_4), filtered, and solvent was removed under reduced pressure to give **2** in 88–91% yield.

Methyl (1,2,3,4,5,6,7,8,9,10-Decahydro-1,8-dioxoacridin-9-yl)acetate (**3**) [22b]. $AcONH_4$ (45.0 mg, 0.59 mmol) was added to a soln. of **2a** (145.0 mg, 0.47 mmol) in CF_3CH_2OH (3 ml). The mixture was stirred continuously at 70° until the reaction was completed after 5.5 h. The solvent was removed under reduced pressure, giving a crude product that was purified by FC producing **3** as pale yellow oil. Yield: 85.0 mg (65%). IR: 3176 (NH), 2946 (CH), 1728 (ester C=O), 1624 (C=O), 1382 (C–N), 1180 (ester C–O). ^{1}H-NMR: 6.27 (*s*, NH); 4.34 (*t*, $J = 5.3$, H–C(9)); 3.57 (*s*, MeO); 2.49–2.27 (complex signal, CH_2(2,4,5,7)); 2.35 (*d*, $J = 5.4$, CH_2COOMe); 2.07–2.01 (complex signal, CH_2(3,6)). ^{13}C-NMR: 196.4 (C=O); 172.6 (ester C=O); 152.5 (C–N); 111.9 (=*C*–C=O); 51.4 (MeO); 39.1 (*C*H_2COOMe); 37.2 (*C*H_2C=O); 27.3 (*C*H_2C=C–C=O); 26.0 (*C*HCH$_2$COOMe); 21.2 (*C*H_2CH$_2$C=O). HR-ESI-MS: 312.1203 ($[M + Na]^+$, $C_{16}H_{19}NNaO_4^+$; calc. 312.1206).

(1,2,3,4,5,6,7,8,9,10-Decahydro-1,8-dioxoacridin-9-yl)acetic Acid (**4**). LiI (0.24 g, 1.76 mmol) was added to a soln. of **3** (85 mg, 0.3 mmol) in anh. AcOEt (3 ml). The mixture was heated under reflux under continuous stirring for 15 h. A second portion of LiI (0.16 g, 1.19 mmol) was added, and the mixture was heated under reflux for 23 h. The solvent was removed under reduced pressure, giving a crude oil which was purified by FC producing **4** as pure colorless oil. Yield: 66%. IR: 3358 (OH), 3302 (NH), 2922 (alkane CH), 1730 (acid C=O), 1620 (C=O), 1600 (C=C), 1259 (C–N), 1180 (C–O), 1112, 1018, 800. ^{1}H-NMR: 5.37 (*s*, NH); 4.09 (*t*, $J = 5.2$, H–C(9)); 2.45–2.23 (complex signal, CH_2(2,4,5,7)); 2.10 (br. *d*, $J = 5.3$, CH_2COOH); 1.96–1.85 (complex signal, CH_2(3,6)). ^{13}C-NMR: 200.8 (C=O); 180.1 (COOH); 156.3 (C–N); 111.6 (=*C*–C=O); 41.8 (*C*H_2COOH); 36.3 (*C*H_2C=O); 26.5 (*C*H_2C=C–C=O); 25.3 (*C*HCH$_2$COOH); 20.4 (*C*H_2CH$_2$C=O). HR-ESI-MS: 314.0791 ($[M + K]^+$, $C_{15}H_{17}KNO_4^+$; calc. 314.0789).

Methyl (10-Benzyl-1,2,3,4,5,6,7,8,9,10-decahydro-1,8-dioxoacridin-9-yl)acetate (**5**). $BnNH_2$ (40.4 mg, 0.38 mmol) was added to a soln. of **2a** (104.2 mg, 0.34 mmol) in anh. benzene (10 ml). The mixture was stirred under reflux for 14 h until the reaction was complete using a flask equipped with a *Dean–Stark* trap. The solvent was removed under reduced pressure, giving a crude product that was purified by FC to give **5** as pure yellow oil fluorescent under UV. Yield: 70%. IR: 2950 (alkane CH), 2360 and 1734 (ester C=O), 1630 (C=O), 1388 (C=N^+), 1176 (ester C–O), 1138. ^{1}H-NMR: 7.33 – 7.16 (*m*, 5 arom. H); 4.84 (*s*, ArCH_2); 4.51 (*t*, *J* = 5.4, H–C(9)); 3.56 (*s*, MeO); 2.62 – 2.22 (complex signal, CH_2(2,4,5,7)); 2.36 (*d*, *J* = 5.3, CH_2COOMe); 1.96 – 1.84 (complex signal, CH_2(3,6)). ^{13}C-NMR: 196.1 (C=O); 172.7 (ester C=O); 154.0 (=C–N); 137.0, 129.3, 127.8, 125.1 (arom. C); 114.1 (=*C*–C=O); 51.3 (MeO); 49.1 (Ar*C*H_2); 39.3 (*C*H_2COOMe); 36.4 (*C*H_2C=O); 26.7 (*C*H_2C=C–C=O); 25.2 (*C*HCH$_2$COOMe); 21.6 (*C*H_2CH$_2$C=O). HR-ESI-MS: 380.1842 ([*M* + H]$^+$, $C_{23}H_{26}NO_4^+$; calc. 380.1856).

Methyl 3-(2-Hydroxy-6-oxocyclohex-1-en-1-yl)-3-(2-{[3-(dimethylamino)propyl]amino}-6-oxocyclohex-1-en-1-yl)propanoate[1]) (**6**). *N,N*-Dimethylpropane-1,3-diamine (39.8 mg, 0.39 mmol) was added to a soln. of **2a** (100.0 mg, 0.32 mmol) in benzene (10 ml). The mixture was stirred under reflux for 13.5 h until complete disappearance of the starting material. The solvent was removed under reduced pressure, giving pure compound **6** as yellow oil after purification by FC. Yield: 52%. IR: 3415 (OH), 3362 (NH), 2943 (alkane CH), 1732 (ester C=O), 1693 (vinylogous acid C=O), 1643 (vinylogous amide C=O in H-bonding system), 1556 (C=C), 1265, 1192 (ester C–O), 1114, 1041. ^{1}H-NMR: 15.03 (*s*, OH); 9.08 (br. *s*, NH); 4.49 (*t*, *J* = 7.5, C*H*CH$_2$COOMe); 3.59 (*s*, MeO); 3.46 – 3.23 (*m*, CH_2NH); 3.23 (*dd*, *J* = 16.9, 7.3, 1 H, CH_2COOMe); 3.00 (*dd*, *J* = 16.9, 7.3, 1 H, CH_2COOMe); 2.72 – 2.14 (complex signal, CH_2(3,3′,5,5′)); 2.37 (*m*, CH_2NMe$_2$); 2.23 (*s*, Me$_2$N); 1.95 – 1.71 (*m*, CH_2(4,4′)); 1.87 (*m*, CH_2CH$_2$NMe$_2$). ^{13}C-NMR: 200.4 (C(6′)); 193.9 (C(2′)); 180.3 (C(6)); 173.5 (*C*OOMe); 169.8 (C(2)); 116.4 (C(1)); 110.5 (C(1′)); 56.4 (*C*H_2NMe$_2$); 51.3 (MeO); 45.4 (Me$_2$N); 41.9 (CH_2NH); 36.3 (C(5′)); 35.7 (*C*H_2COOMe); 35.1 (C(5)); 31.4 (C(3′)); 27.4 (*C*H_2CH$_2$NMe$_2$); 26.7 (*C*HCH$_2$COOMe); 26.2 (C(3)); 20.5 (C(4′)); 20.2 (C(4)). HR-ESI-MS: 415.2192 ([*M* + Na]$^+$, $C_{21}H_{32}N_2NaO_5^+$; calc. 415.2203).

Methyl 3-[2-(Benzylamino)-6-oxocyclohex-1-en-1-yl]-3-(2-hydroxy-6-oxocyclohex-1-en-1-yl)propanoate (**7**). $BnNH_2$ (30.6 mg, 0.29 mmol) was added to a soln. of **2a** (91.0 mg, 0.29 mmol) in EtOH (1 ml). The mixture was heated, and the temp. was kept between 40 and 50° with continuous magnetic stirring for 8 h until complete disappearance of the reagent. The solvent was removed under reduced pressure, giving a crude product that was purified by FC to give **7** as colorless oil. Yield: 32.0 mg (63%). IR: 3265 (OH), 3144 (NH), 2947 (alkane CH), 1736 (ester C=O), 1730 (vinylogous acid C=O), 1620 (C=C, NH H-bonding), 1583 (C=C coupled with C–N), 1573 (vinylogous amide C=O in H-bonding systems), 1433 and 1408 (C=N^+ conjugated with C=C), 1306 and 1259 (C–N free and associated amides), 1199 (C–O). ^{1}H-NMR: 14.69 (*s*, OH); 9.57 (*s*, NH); 7.31 – 7.17 (*m*, 5 arom. H); 4.55 (*t*, *J* = 7.5, C*H*CH$_2$COOMe); 4.46 (*t*, *J* = 6.4, CH_2NH); 3.53 (*s*, MeO); 3.24 (*dd*, *J* = 16.1, 6.9, 1 H, CH_2COOMe); 2.90 (*dd*, *J* = 16.1, 6.9, 1 H, CH_2COOMe); 2.54 – 2.01 (complex signal, CH_2(3,3′,5,5′)); 1.86 – 1.54 (complex signal, CH_2(4,4′)). ^{13}C-NMR: 200.7 (C(6′)); 195.0 (C(6)); 180.1 (C(2)); 173.4 (*C*OOMe); 169.9 (C(2′)); 137.5, 128.9, 127.5, 126.6 (arom. C); 116.7 (C(1)); 111.1 (C(1′)); 51.4 (MeO); 47.1 (CH_2NH); 36.3 (C(5′)); 35.7 (CH*C*H$_2$COOMe); 35.2 (C(5)); 31.3 (C(3′)); 26.8 (*C*HCH$_2$COOMe); 26.1 (C(3)); 20.5 (C(4′)); 20.2 (C(4)). HR-ESI-MS: 398.1951 ([*M* + H]$^+$, $C_{23}H_{28}NO_5^+$; calc. 398.1962).

Methyl 3-(2-Amino-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)propanoate (**8**). Crude **2b** obtained by microwave-assisted *Michael–Michael* reaction was dissolved in MeOH/AcOH 9 : 1 (10 ml), and $BnNH_2$ (1.06 mmol, 0.12 ml) was added. The mixture was stirred at 80° in the microwave reactor until complete conversion of **2b**. After 15 min, the solvent was removed under reduced pressure, giving **8** as yellow oil after careful purification along with non-identified products. Yield: 40%. IR: 3450 (NH H-bonding), 2926 (alkane CH), 1738 (ester C=O), 1679 (vinylogous acid C=O in H-bonding system), 1643 (NH H-bonding), 1632 (vinylogous amide C=O in H-bonding system), 1613 (C=C), 1597 (C=C), 1146 (ester C–O). ^{1}H-NMR: 9.28 (*s*, NH); 8.01 (*s*, OH); 4.34 (*t*, *J* = 6.3, C*H*CH$_2$COOMe); 3.63 (*s*, MeO); 3.27 (*dd*, *J* = 17.0, 7.5, 1 H, CH_2COOMe); 3.15 (*dd*, *J* = 16.7, 7.6, 1 H, CH_2COOMe); 2.70 (*s*, CH_2(3)); 2.40 (*s*, CH_2(3′)); 2.34 (*s*, CH_2(5)); 2.11 (*s*, CH_2(5′)); 1.13, 1.12 (*s*,

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[1]) The C-atoms in the vinylogous acid unit were designated as C(1), C(2), *etc.*, and those in the vinylogous amide unit as C(1′), *etc.*

2 Me); 1.02, 1.01 (*s*, 2 Me). ^{13}C-NMR: 199.0 (C(6′)); 193.5 (C(6)); 172.8 (*C*OOMe); 165.3 (C(2)); 136.3 (C(2′)); 114.5 (C(1′)); 112.4 (C(1)); 51.1 (MeO); 50.5 (C(5′)); 43.4 (C(5)); 41.4 (C(3′)); 34.7 (C(3)); 32.7 (*C*H$_2$COOMe); 31.4 (C(4′)); 30.8 (C(4)); 29.7 (Me); 29.0 (Me); 28.6 (Me); 28.2 (Me); 27.1 (*C*HCH$_2$COOMe). HR-ESI-MS: 386.1668 ([*M* + Na]$^+$, $C_{20}H_{29}NNaO_5^+$; calc. 386.1938).

Methyl 3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-3-(2-{[3-(dimethylamino)propyl]-amino}-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)propanoate (**9**). A soln. of dimedone derivative **2b** (103.3 mg, 0.28 mmol) in benzene (10 ml) was added in a flask containing a *Dean–Stark* trap. *N*,*N*-Dimethylpropane-1,3-diamine (31.8 mg, 0.31 mmol) was added. The mixture was magnetically stirred under reflux for 8.5 h until complete disappearance of the reagent. The solvent was removed under reduced pressure, giving the crude product that was subsequently purified by FC to give pure compound **9** as yellow oil. Yield: 58.3 mg (61%). IR: 3474 (OH), 3278 (NH), 2956 (alkane CH), 1733 (ester C=O), 1688 (vinylogous acid C=O in H-bonding system), 1640 (NH H-bonding), 1611 (C=C), 1635 and 1605 (vinylogous amide C=O in H-bonding system), 1146 (ester C–O). ^{1}H-NMR: 14.62 (*s*, OH); 8.75 (br. *s*, NH); 4.48 (*t*, *J* = 7.6, C*H*CH$_2$COOMe); 3.53 (*s*, MeO); 3.41 – 3.20 (*m*, C*H*$_2$NH); 3.24 (*dd*, *J* = 16.1, 7.3, 1 H, C*H*$_2$COOMe); 2.97 (*dd*, *J* = 16.1, 7.2, 1 H, C*H*$_2$COOMe); 2.39 – 2.11 (complex signal, CH$_2$(3,3′,5,5′)); 2.33 (complex signal, C*H*$_2$NMe$_2$); 2.20 (*s*, Me$_2$N); 1.81 (*m*, C*H*$_2$CH$_2$NMe$_2$); 1.01 (*s*, Me); 0.98 (*s*, Me); 0.94 (*s*, 2 Me). ^{13}C-NMR: 199.6 (C(6′)); 193.0 (C(6)); 177.9 (C(2′)); 173.4 (*C*OOMe); 167.9 (C(2)); 115.3 (C(1′)); 109.2 (C(1)); 56.5 (*C*H$_2$NMe$_2$); 51.4 (MeO); 49.9 (C(5′)); 48.6 (C(5)); 45.4 (Me$_2$N); 44.7 (C(3′)); 41.9 (CH$_2$NH); 39.5 (C(3)); 35.2 (*C*H$_2$COOMe); 31.1 (C(4′)); 30.7 (C(4)); 30.3 (Me); 29.9 (Me); 27.4 (*C*H$_2$CH$_2$NH); 26.3 (*C*HCH$_2$COOMe); 26.2 (Me). HR-ESI-MS: 449.3010 ([*M* + H]$^+$, $C_{25}H_{41}N_2O_5^+$; calc. 449.3010).

Methyl 3-[2-(Benzylamino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl]-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)propanoate (**10**). BnNH$_2$ (0.017 ml) was added to a soln. of **2b** (50 mg, 0.16 mmol) in MeOH/AcOH 9 : 1. The mixture was stirred at 60° in the microwave reactor until complete conversion of **2b**. After 15 min, the solvent was removed under reduced pressure, and the crude product was purified by FC to give **10** as colorless oil. Yield: 73%. IR: 3271 (OH), 3154 (NH), 2954 (alkane CH), 2830 (MeO), 1735 (ester C=O), 1662 (C=C, NH H-bonding), 1581 (C=C coupled with C–N), 1408 (C=N$^+$ conjugated with C=C), 1273 (C–N free and associated amides), 1165 (C–O). ^{1}H-NMR: 14.36 (*s*, OH); 9.32 (*s*, NH); 7.32 – 7.35 (*m*, 5 arom. H); 4.65 (*t*, *J* = 7.5, C*H*CH$_2$COOMe); 4.53 (*t*, *J* = 5.1, C*H*$_2$NH); 3.60 (*s*, MeO); 3.39 (*dd*, *J* = 16.1, 6.8, 1 H, C*H*$_2$COOMe); 2.96 (*dd*, *J* = 16.1, 8.4, 1 H, C*H*$_2$COOMe); 2.38 – 2.30 (complex signal, CH$_2$(4,4′)); 2.28 (complex signal, CH$_2$(2,2′)). ^{13}C-NMR: 200.0 (C(6′)); 194.3 (C(6)); 177.8 (C(2)); 173.4 (*C*OOMe); 168.0 (C(2′)); 137.7, 128.8, 127.5, 126.6 (arom. C); 115.5 (C(1)); 109.9 (C(1′)); 51.5 (MeO); 50.0, 48.8 (C(5,5′)); 47.0 (CH$_2$NH); 44.7 (C(3)); 39.2 (C(3′)); 35.6 (CH*C*H$_2$COOMe); 31.2 (C(4)); 30.9 (C(4′)); 30.0, 29.6, 26.2, 26.0 (Me); 26.6 (*C*HCH$_2$COOMe). HR-ESI-MS: 476.2407 ([*M* + Na]$^+$, $C_{27}H_{35}NNaO_5^+$; calc. 476.2407).

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