A Synthetic approach to PW2-like compounds

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Abstract: The 9H-xanthene derivatives, like PW2, displayed a wide spectrum of bioactivities. Herein, we reported a rapid and simple synthetic route for compounds containing the xanthenic moiety in their structure and amides. The efficient preparation of novel 1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1-xanthen-9-yl- acetic acid alkyl esters by multicomponent tandem Michael-cyclization reactions starting from cyclohexanediones and alkynes. Iodine and cerium (IV) ammonium nitrate were used for the oxidative aromatization step proving a series of 1,8-mono and dialkoxy-alkyl-xanthenyl-9-yl acetic acid esters in good yields. The proposed mechanism for the oxidative aromatization involves several organic transformations. The final step was the incorporation of an amide to mimic the PW2 structure that was prepared by hydrolysis of the esters, followed by the amides formation using *N,N*-dimethyl-1,3- propandiamine, and benzylamine.

Introduction

Molecules such as linear tricycles are ideal skeletons to produce a wide range of drugs for diverse clinical applications. Interconnected ring systems, orientation, aromaticity and heteroatoms are responsible of the ability to bind different receptors that provide a wide spectrum of bioactivities.[1–4] Between them, xanthene derivatives present different activities including antibacterial,[5] antiviral,[6] antimalarial [7] and anti-inflammatory.[8]

9*H*-xanthene derivatives, like PW2, PW3, WU5 and WU6 (Figure 1), are interesting examples of this scaffold displaying antiparasitic activity, in particular toward *Plasmodium falciparum*, malaria etiological agent.[7]

9,9-Dimethylxanthene derivatives recently reported by Chibale *et al* have shown antikinetoplastid activity against *Trypanosoma cruzi*, *Trypanosoma brucei*, and *Leishmania donovani*, Figure 1.[9]

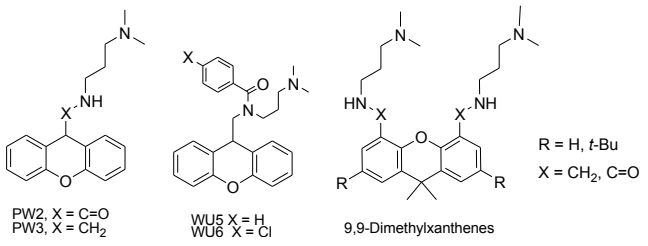


Figure 1. Synthetic 9*H*-xanthenes, chloroquine resistance-reversing agents.

We previously reported the synthesis of several octahydroxanthenodiones by a *tandem* Michael-Michael-Cyclization reaction of 1,3-cyclohexanediones, methyl propiolate, L-proline and iodine, either in solution or in solid phase.[10–13]

Molecular iodine has played an important role in organic synthesis,[14] being an expedient old reagent for different chemical transformations.[15,16] Among its numerous applications, we found the systematic functionalization of Hagemann's ester derivatives that permitted the preparation of highly substituted phenols and benzenes according to Kotnis method.[17] Likewise, the reaction of iodine in methanol was extended to prepare substituted resorcinols (olivetol) from 1,3-cyclohexanedione, and cyclohexane-1,3-diones with electron withdrawing substituents at the 2-position. The corresponding mono-methoxy resorcinol derivatives were obtained as the major products,[18] or the substituted 2-iodomethyl- tetrahydrobenzofuran-4-ones from α-allyl-cyclohexane-1,3-diones ones.[19]

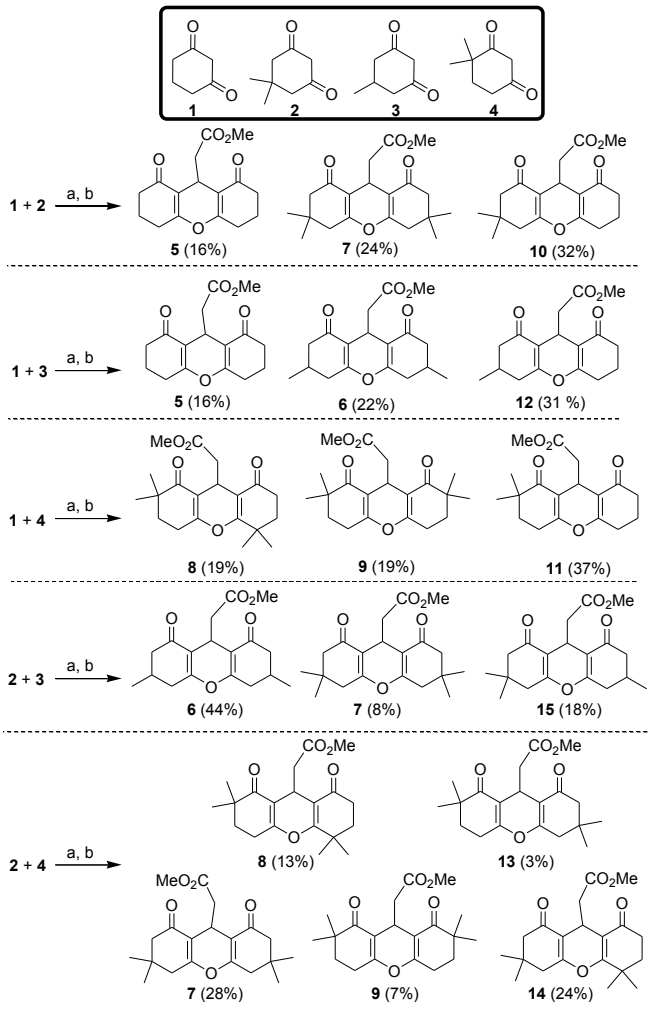
Their synthetic utility can also be illustrated by reactions of 2-cyclohexenones with electron withdrawing group in the 4-position or *N*-alkyl-1,3-cyclohexadien-1-amines with iodine and sodium alkoxide undergoing regioselective iodination and aromatization.[20]

Herein, we present the synthesis of a new series of non-symmetric hydro-xanthenodiones. The oxidative aromatization of the lateral rings of the heterocyclic core was also studied, being an efficient, user-friendly procedure to generate structurally diverse structures.[21,22] Moreover, the collection of derivatives was extended preparing different amides, of high incidence in modern pharmaceuticals and biologically active compounds,[23] by reaction of the xanthenic precursors with different amines.

Results and Discussion

First, we looked to expand the scope of the Michael reaction focusing on non-symmetric structures. Different 1,3-cyclohexanediones were combined to introduce structural diversity in the tricycle by means of multicomponent reactions (MCR) in solution. The reaction of 1,3-cyclohexanediones **1**-**4**, methyl propiolate and L-proline in DMSO at room temperature and subsequent I_2/EtOH addition afforded the symmetric and the non-symmetric esters **5**-**15** in 69-77% overall yields. (Scheme 1) The 1,3-cyclohexanedione **4**, that has a non-symmetrical substitution, leads to more products than the rest of the diones.

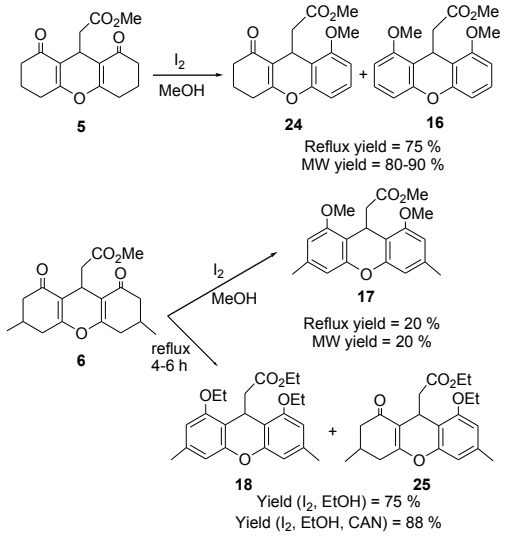
Then, the oxidative aromatization of the lateral rings of the heterocyclic core of **5**-**15** using molecular iodine in an alcohol solution was evaluated.



Scheme 1. Three-component synthesis of xanthenedione esters **5**-**15**. a) Methyl propiolate, DMSO, RT, 13 days; b) I_2, MeOH or EtOH, 5 h.

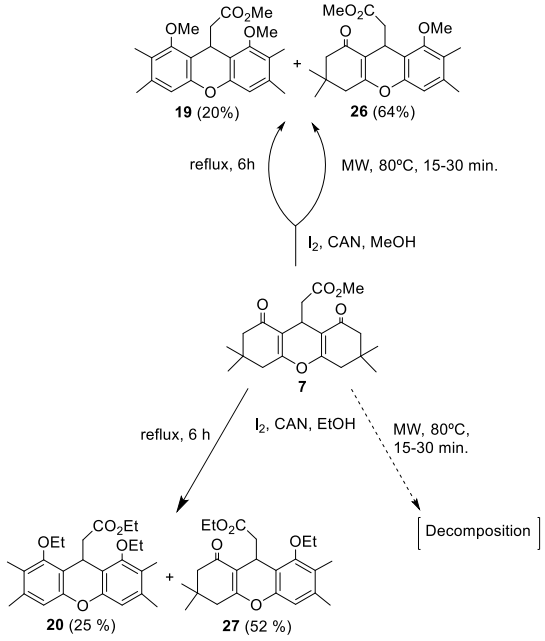
The cyclohexenone portions of ester **5** undergone aromatization with iodine in refluxing methanol, being the di-oxidized ester **16** the major product, along with small amount of **24** in 75% overall yield. (Scheme 2) Alternatively, a one-pot reaction of **5** with iodine in methanol under microwave heating for 15-30 minutes provided a mixture of **24:16** in a 1:2 ratio with high yields (80-90%). The reaction of the mono-substituted cyclic ketone **6** in methanol, which was less reactive than **5**, provides the dimethoxy methyl ester **17** as only isolated product, but in low yields.

The oxidative aromatization in ethanol also produce the concomitant transesterification of the methyl acetate side chain. The addition of a catalyst such as the cerium (IV) ammonium nitrate (CAN),[24,25] to the iodine increased the overall yield of ethyl esters **18** and **25**. (Scheme 2).



Scheme 2. Oxidative reactions on **5** and **6** with iodine.

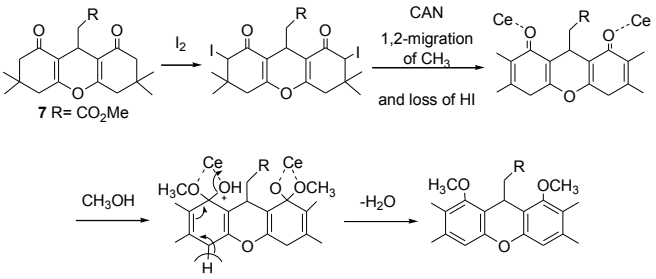
In order to carried out the oxidation of the *gem*-dimethyl-ester **7,** the reaction with iodine in methanol or ethanol needed CAN as catalysis, due to the lower reactivity of this substrate. Consequently, mixtures of methoxy-methyl-esters **19** (20%) and **26** (64%) and the corresponding ethoxy-ethyl-esters **20** (25%) and **27** (52%) were successfully separated during the purification by column chromatoghraphy. (Scheme 3)



Scheme 3. Reactions of **7** with iodine, CAN, MeOH or EtOH.

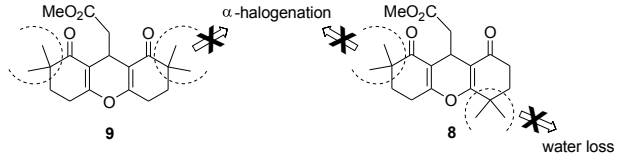
A possible mechanism for the oxidation of compound **7** is shown on Scheme 4. The addition of iodine, gives a product of α-halogenation which undergoes a 1,2- migration of a methyl group with addition of the catalyst generating a double cross-conjugation in both cyclohexanone portions by the loss of hydrogen iodide.

Water is then removed after addition of methanol (or ethanol) to the carbonyl group, and thus emerging the aromatic products.[24]



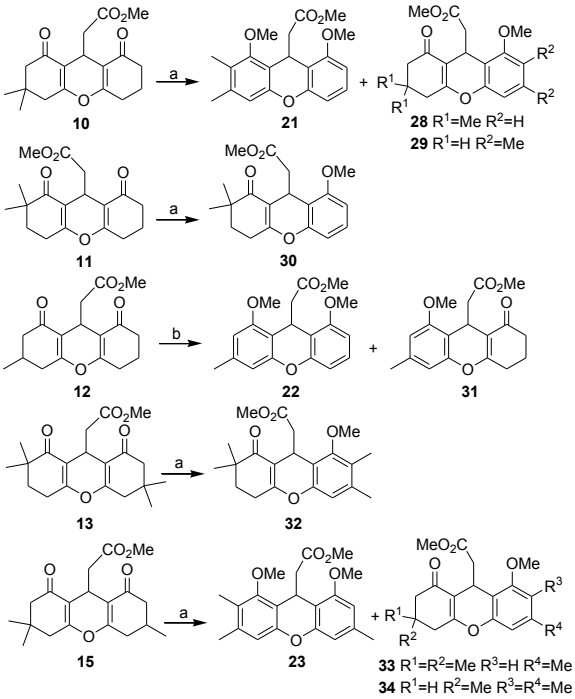
Scheme 4. Reaction mechanism of the compound **7** with iodine-cerium (IV) ammonium nitrate in methanol.

When same oxidative aromatization condition were applied on *gem*-dimethyl-ester **8** and **9**, the reaction do not provide the expected products. That was not unexpected based on the proposed reaction mechanism, where the α-halogenation and water loss are not possible. (Scheme 5)



Scheme 5. Impeded reaction positions for α-halogenation and water loss.

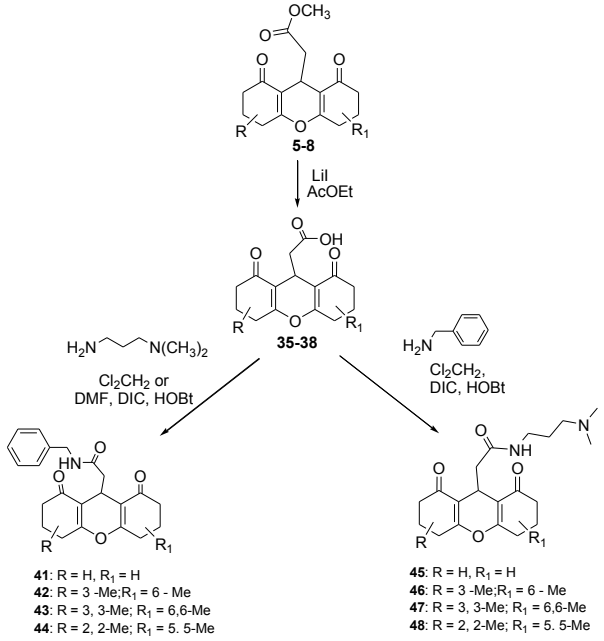
As is shown in Scheme 6, the oxidation of the non-symmetric compounds **11**-**15** has also been studied. These reactions gave different mixtures of products depending on the particular ring substitution and if the aromatization occurs in one ring or both.



Scheme 6. Oxidation reactions of non symmetric compounds **10-15** with iodine-cerium (IV) ammonium nitrate in methanol. a) I_2, CAN, MeOH; b) I_2, MeOH

Reactions carried out on compounds **11** and **13** give only products of mono-oxidation on the annular portion because one of the α-position to the carbonyl groups is blocked. Unfortunately, after different attempts, the isolation of the oxidation product of compound **14,** that was expected to produce a mono-oxidized derivative, was unsuccessful.

As was mentioned before, we aim to prepare xanthenic amides derivaties that mimic PW2. Based on the previous experience of our group, the esters were transformed in carboxylic acids followed by amides formation using *N*-(3-(dimethylamino)propyl)amine and benzylamine. Esters **5-8** showed a low reactivity with standard reagents like aqueous LiOH, NaOH or KOH. To surpass that problem, the acids **35**-**38** were demethylated with LiI in EtOAc under reflux.[26] Thus, **35**-**38** were transformed into the *N*-benzyl amides **41-44** and *N*-(3-(dimethylamino)propyl) amides **45-48** by reaction with the amines with the corresponding acids, HOBt, and carbodiimide in dichlorometane. The mixture was maintained at 0°C during 1.5 hours and them warm up to room temperature. (Scheme 7) and the purification by column chromatography the amides were obtained with 53-95% yield.

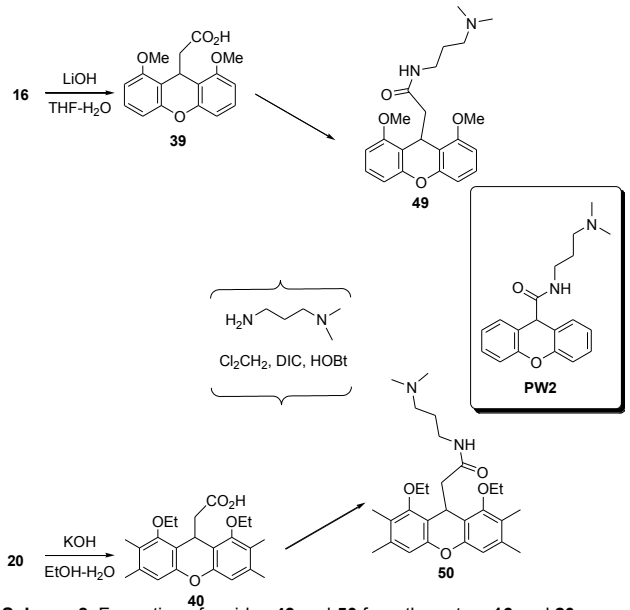


Scheme 7. Formation of amides **41-48** from the carboxylic acid **35-38**

All the attempts of oxidative aromatization of amides were unsuccessful. Therefore, we decided to reach the aromatic amides **49** and **50** starting from the aromatic esters **16** and **20** through the corresponding carboxylic acids. (Scheme 8)

The acid **39** was obtained by hydrolysis using LiOH as a base, on the other hand, to hydrolyze the ester **20,** the base had to be change by KOH since the ethyl ester did not react with LiOH.

The amides **49** and **50** were prepared and purified in a similar way than the amides **45-48** with a global yield of 50-60%.



Scheme 8. Formation of amides **49** and **50** from the esters **16** and **20**

Conclusions

We have successfully developed a rapid and simple synthetic route for the efficient preparation of a series of 1,8-dioxo-2, 3, 4, 5, 6, 7, 8, 9-octahydro-1H-xanthene -9-yl acetic acid esters **5**-**15** by multicomponent Michael-Michael-cyclization reactions.

Molecular iodine promotes both cyclization and aromatization reactions contributing to an extension of the iodine methodology towards the formation of more complex structures.

Iodine-mediated oxidative aromatization of 1,8-dioxo-hydroxanthene scaffold is a simple synthetic procedure for obtaining mono- and dialkoxy-xanthenyl-9-yl acetic acid esters **16**-**34.** This oxidative aromatization involves different transformations including α-iodination, transesterification, etherification, elimination and alkyl rearrangement when it was required. Applying the reaction on non-symmetric tricycles was crucial to validate the proposed mechanism.

The final approach was to incorporate amides on the structure to mimic PW2. Compounds **49** and **50** were prepared from the corresponding acids **39** and **40** applying the same methodology used to prepared the amides **45**-**48**.

This diversity oriented synthesis strategy will be used as the starting point of a medicinal chemistry program targeting neglected tropical diseases.

Experimental Section

General. All reactions involving air or moisture-sensitive materials, were carried out under nitrogen. Flash chromatography was performed with 300-400 mesh silica gel under slight nitrogen pressure, with increasing gradients of solvent mixtures. All chemicals and solvents are commercially available and were used after purification according to Armarego and Chai.[27] IR spectra were recorded with a Shimadzu, Prestige 21 Model spectrophotometer, with samples as liquid films in NaCl for oils. NMR experiments were run in $CDCl_3$ at 300.13 MHz for ^1H NMR and at 75.4 MHz for ^{13}C NMR with a Bruker Avance-300 MHz NMR spectrometer and the corresponding solvent as internal reference standard. High-resolution mass spectrometry was carried out with a LC-QTOf Bruker MicroTOF QII. Microwave heating was performed in a CEM Discover® System using septum-sealed 10 mL vials for high-pressure reaction conditions with stirring and IR-monitored temperature control. Melting points (uncorrected) were measured in open capillary tubes with an Electrothermal 9100 apparatus. HPLC experiments were performed with a Hewlett Packard series 1100 system with C_{18} and Chiradex columns. Detection wavelength was set at 215 nm, ref: 360 and the column was isocratically eluted with MeOH: H_2O 75:25 for C18 and 60:40 for Chiradex columns, 0.7 mL min^{-1}, *c* 2.0 mg mL^{-1}. Optical rotations were determined using a JASCO DIP-1000 digital polarimeter in 100 mm cells and the sodium D line (589 nm) at temperature in solvent and concentration indicated.

Preparation of esters 5-15 (MCR): 2.2 mmol of dione mixture and L-Pro (16 mg, 6 mol% per 1.1 mmol of dione) were dissolved in DMSO (6 mL) and methyl propiolate (0.08 mL, 1 mmol) was added. The reaction mixture was then left for 13 days at room temperature. Finally, NH_4Cl (1 mL) was added. The aqueous phase was extracted with EtOAc (2 x 3 mL) and the organic phase was dried with anhydrous Na_2SO_4, filtered and solvent removed under reduced pressure. For cyclization, a solution of atropisomers crude (0.5 mmol) and iodine (3 mol%) in anhydrous EtOH (1.25 mL) was stirred at room temperature. The reaction mixture was monitored by TLC and completed in 5 h. The solvent was removed *in vacuo*, and the residue was taken up in CH_2Cl_2 (10 mL) and washed with sodium thiosulphate solution (2 x 10 mL), brine, and water. The combined organic layer was dried with anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to furnish hydroxanthenes. The residue was purified by flash chromatography using hexane/EtOAc/EtOH gradients.

Preparation of xanthenes by iodine oxidation: A solution of hydroxanthene crude (0.5 mmol) and iodine (635 mg, 2.5 mol) in anhydrous EtOH or MeOH (3 mL) was refluxed with continuous stirring until complete conversion. The solvent was removed *in vacuo*, and the residue was taken up in CH_2Cl_2 (10 mL) and washed with sodium thiosulphate solution (2 x 10 mL), brine, and water. The organic layer was dried with anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to furnish xanthenes. If it is necessary to add CAN as catalyst (0.05 mmol, 10 mol %).

Preparation of xanthenes by microwave-assisted iodine oxidation: A solution of hydroxanthene (0.16 mmol) in anhydrous EtOH (3 mL) was added into an oven-dried, 10 mL pressure-rated reaction vial equipped with a stirring bar. Then, iodine (203 mg, 0.80 mmol) were added. The resulting solution was stirred at 80^0C in the microwave reactor until complete conversion. After that, the solvent was removed under reduced pressure, and the crude was dissolved in ethyl acetate (3 mL) and washed with sodium thiosulphate solution (2 x 5 mL), brine, and water. The organic layer was dried with anhydrous Na_2SO_4 and filtered, and the solvent was removed under vacuum to furnish the product. If it is necessary to add CAN as catalyst (0.016 mmol, 10 mol%).

Demethylation of esters. Preparation of carboxylic acids 35-38. LiI (1.6 mmol) was added to a solution of the ester parent (0.16 mmol) in anhydrous EtOAc (1.6 mL). The mixture was refluxed with continuous stirring until complete conversion. Then it was washed with 10% $Na_2S_2O_3$ until disappearance of the red color. The mixture was acidified to pH= 4 with 2N HCl. The phases were separated; the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvent was removed under vacuum.

Preparation of the amides 41-44. To a solution of benzylamine (0.142 mL, 1.3 mmol) in anhydrous dichloromethane (1 mL), the acid (1 mmol) dissolved in dichlorometane (2.5 mL) and HOBt (133 mg, 1 mmol) were added. The mixture was cooled to 0°C.

1 mmol of diisopropylcarbodiimide (DIC) (for **41**) or dicyclohexylcarbodiimide DCC (for **42-44**) was then added and left with

magnetic stirring during 90 minutes at room temperature. The formation of a solid was observed. The solvent was removed *in vacuo* and the crude was dissolved in THF (2 mL) produced the urea by-product precipitation. This precipitate led to the modification of the method which solid was filtered and washed with THF (3 x 1 mL). The organic phase was concentrated under reduced pressure and the crude that was purified by column chromatography (Hexane/EtOAc, 45:55) gave the amides with good yield.

Preparation of the amides 45-50. To the amine solution (1.3 mmol) in anhydrous Cl_2CH_2 (3.5 mL), acid (1 mmol) and the HOBt (1 mmol) were added. The mixture was cooled to 0°C in an ice bath and was slowly added the DIC (57.1 mg, 1.2 mmol) and left with magnetic stirring during 90 minutes. Passed this time, the mixture was left at room temperature with stirring for 24 hours. Reaction solvent was removed under reduced pressure and the product was purified by column chromatography with solvents mixture (Cl_2CH_2/MeOH 80:20). Yield: 77 - 94%.

Note: The esters compounds **5-7** and **9** were obtained and described in *ref.* 15b

Methyl (2,2,5,5-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (8)

Yield 42%. Hex:EtOAc 70 : 30. White solid. Mp: 99.2-99.7 °C. $\alpha_D^{20.8°}$= +3.71 (c 0.55, $CHCl_3$). HPLC: t_R = 5.34 min., C_{18} (MeOH/H_2O 75: 25); Chiradex (MeOH/H_2O 60: 40), t_R = 8.49 min. and t_R = 12.90 min.

IR (film): 2962, 2868 (C-H), 1732 (C=O ester), 1664 (C=*O*), 1618 (C=C), 1381, 1177, 1164, 1068 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.92 (t, *J* = 4.4 Hz, 1H, 9-H), 3.53 (s, 3H, OCH_3), 2.60 (dt, *J* = 6.8 Hz, 2H, 4-H), 2.55 (d, *J* = 4.4 Hz, 2H, C*H*$_2$COOCH$_3$), 2.44 (dd, *J* = 6.1, 6.7, 7.3 Hz, 2H, 7-H), 1.93-1.79 (m, 4H, 3-H, 6-H), 1.28 (s, 3H, 5-CH_3), 1.22 (s, 3H, 5-CH_3), 1.13 (s, 3H, 2-CH_3), 1.09 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, CDCl3, 25°C, TMS): δ = 201.7 ((CH$_3$)$_2$CH*C*=O), 196.7 (C=O), 172.2 (*C*OOCH$_3$), 170.9 (4b-C), 164.0 (4a-C), 112.4 and 112.0 (8a-C, 8b-C), 51.1 (OCH_3), 40.4 (2-C), 37.0 (*C*H$_2$COOCH$_3$), 35.4 (6-C), 34.4 (5-C), 34.1 (7-C), 33.8 (3-C), 26.2 (5-CH_3), 24.5 (2-CH_3), 24.4 (5-CH_3), 24.1 (2-CH_3), 24.1 (9-C), 24.0 (4-C).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{20}H_{26}NaO_5$: 369.16725; found: 369.16724.

Methyl (3,3-dimethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (10) was obtained as acid-derivative following the synthetic sequence of reactions on solid phase, followed by esterification as we previously reported.[12]

Methyl (2,2-dimethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (11).

Yield: 37%. Pale yellow oil. HPLC: t_R = 5.40 min., C_{18}, MeOH:H_2O 75 : 25.

IR (film): 2951, 2870 (C-H), 1732 (C=O ester), 1660 (C=*O*), 1622 (C=C), 1381, 1175, 1130, 1020, 952, 933 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.92 (t, *J* = 4.3 Hz, 1H, 9-H), 3.54 (s, 3H, OCH_3), 2.58 (d, *J* = 4.3 Hz, 2H, C*H*$_2$COOCH$_3$), 2.52 (m, 2H, 4-H), 2.46-2.42 (m, 4H, 5-H, 7-H), 2.02 (m, 2H, 3-H), 1.85 (m, 2H, 6-H), 1.12 (s, 3H, CH_3), 1.08 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS)): δ = 201.9 ((CH$_3$)$_2$CH*C*=O), 197.2 (C=O), 172.4 (*C*OOCH$_3$), 165.9 (4a-C), 163.9 (4b-C), 114.1(9a-C), 112.3 (8a-C), 51.2 (OCH_3), 40.5 (2-C), 37.0 (7-C), 36.6 (*C*H$_2$COOCH$_3$), 34.8 (4-C), 27.2 (5-C), 24.2 (3-C), 24.1 (*C*H$_3$), 24.0 (*C*H$_3$), 23.7 (9-C), 20.4 (6-C).

HRMS (ESI): *m/z* [M+H]$^+$ calcd. for $C_{18}H_{23}O_5$: 319.1545; found: 319.1540.

Methyl (3-methyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (12).

Yield: 31%. Pale yellow oil. [α_D^{20}] +0.22, [α_D^{21}] +0.98 (*c* 1.1, $CHCl_3$). HPLC: t_R = 4.72 min., C_{18}, MeOH:H_2O 75 : 25, t_R 3.68, 5.0 min., Chiradex, (MeOH/H_2O 60: 40).

IR (film): 2953, 2875 (C-H), 1730 (C=O ester), 1660 (C=O), 1620 (C=C), 1383, 1182, 1132, 1024, 985, 949, 850, 756 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.92 (t, *J* = 4.4 Hz, 1H, 9-H), 3.54 (s, 3H, OCH_3), 2.61 (d, *J* = 4.3 Hz, 2H, C*H*$_2$COOCH$_3$), 2.64-2.09 (m, 8H, 2-H, 4-H, 5-H, 7-H), 2.01 (m, 3H, 3-H, 6-H), 1.09 (d, *J* = 2.7 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.1 and 197.0 (C=O), 172.3 (*C*OOCH$_3$), 166.0 (4a-C), 165.6 (4b-C), 114.3 (9a-C), 113.8 (8a-C), 51.2 (OCH_3), 45.3 (4-C), 45.0 (7-C), 37.1 (*C*H$_2$COOCH$_3$), 37.0 (2-C), 35.3 (5-C), 28.1 (3-C), 23.7 (9-C), 20.8 (*C*H$_3$), 20.4 (6-C).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{17}H_{20}NaO_5$: 327.12084; found: 327.12029.

Methyl (2,2,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (13).

Yield: 3 %. Yellow oil. HPLC: t_R = 5.34 min., C_{18}, (MeOH/H_2O 75: 25), t_R = 8.50, 12.93 min., Chiradex, (MeOH/H_2O 60: 40).

IR (film): 2960, 2860 (C-H), 1730 (ester), 1662 (C=C–*C*=*O*), 1620 (C=C), 1450, 1380, 1200, 1175, 1160, 930, 770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.88 (bs, 1H, 9-H), 3.52 (s, 3H, OCH_3), 2.65 (dd, *J* = 4.2 Hz, 1H, C*H*$_2$CO$_2$CH$_3$), 2.50 (dd, *J* = 4.1 Hz, 1H, C*H*$_2$CO$_2$CH$_3$), 2.86 (s, 2H, 7-H), 2.60-2.30 (m, 4H, 4-H, 5-H), 1.82 (m, 2H, 3-H), 1.29 (s, 3H, 2-CH_3), 1.27 (s, 3H, 2-CH_3), 1.08 (s, 3H, 6-CH_3), 1.07 (s, 3H, 6-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 201.9 (1-C=O), 197.1 (8-C=O), 172.4 (*C*OOMe), 164.7 (4a-C), 164.5 (4b-C), 112.9 (9a-C), 113.0 (8a-C), 51.2 (OCH_3), 50.8 (5-C), 40.8 (7-C), 36.3 (*C*H$_2$COOMe), 35.4 (2-C), 34.0 (3-C), 32.0 (6-C), 29.5 (6-CH_3), 26.9 (6-CH_3), 24.5 (2-CH_3), 24.3 (4-C), 24.1 (9-C), 23.8 (2-*C*H$_3$).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{20}H_{26}NaO_5$: 369.16725; found: 369.16623.

Methyl (3,3,5,5-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (14).

Yield: 24%. Yellow oil. HPLC: t_R = 4.32 min., C_{18}, (MeOH/H_2O 75: 25), t_R 4.81, 6.86 min., Chiradex, (MeOH/H_2O 60: 40).

IR (film): 2959, 2860 (C-H), 1728 (C=O ester), 1662 (C=C–*C*=*O*), 1615 (C=C), 1450, 1380, 1175, 1161, 1070, 925, 770 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.94 (t, *J* = 4.2 Hz, 1H, 9-H), 3.51 (s, 3H, OCH_3), 2.60 (dd, *J* = 4.1 Hz, 2H, C*H*$_2$CO$_2$CH$_3$), 2.44 (t, *J* = 6.2 Hz, 2H, 7-H), 2.35 (s, 2H, 4-H), 2.25 (s, 2H, 2-H), 1.85 (m, 2H, 6-H),

1.23 (s, 3H, 5-CH_3), 1.20 (s, 3H, 5-CH_3), 1.10 (s, 3H, 3-CH_3), 1.09 (s, 3H, 3-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.0 (1-C=O), 196.8 (8-C=O), 171.0 (COOMe), 164.7 (4b-C), 164.0 (4a-C), 112.6 (9a-C), 112.2 (8a-C), 51.3 (OCH_3), 50.7 (4-C), 40.7 (2-C), 37.0 (*C*H_2COOMe), 35.3 (6-C), 34.5 (5-C), 33.8(7-C), 32.0 (3-C), 29.5 (3-*C*H_3), 26.8 (3-*C*H_3), 26.2 (5-CH_3), 24.6 (5-CH_3), 23.8 (*C*HCH_2COOMe).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{20}H_{26}NaO_5$: 369.16725; found: 369.16727.

Methyl (3,3,6-trimethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)acetate (15).

Yield: 9%. Yellow oil. HPLC: t_R = 4.53 min., $C_{18,}$ (MeOH/H_2O 75: 25), Chiradex, t_R 4.65, 7.30 min., (MeOH/H_2O 60: 40).

IR (film): 2954, 2874 (C-H), 1732 [*C(O)*–OMe], 1666 (C=C–*C*=*O*), 1622 (C=C), 1381, 1192, 1134, 1028, 1005, 825 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.87 (bs, 1H, 9-H), 3.51 (s, 3H, OCH_3), 2.61 (dd, *J* = 2.3, 4.1 Hz, 2H, C*H*$_2$CO$_2$CH$_3$), 2.58 (m, 2H, 7-H), 2.49 (d, *J* = 3.8 Hz, 2H, 5-H), 2.34 (s, 2H, 4-H), 2.19 (s, 2H, 2-H), 2.04-1.92 (m, 1H, 6-H), 1.06 (bs, 9H, 3-*gem* CH_3, 6-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.2 (1-C=O, 8-C=O), 172.4 (*C*O$_2$CH$_3$), 166.1 (4b-C), 164.5 (4a-C), 113.8 and 113.2 (=*C*C=O), 51.2 (OCH_3), 50.8 (2-C), 45.3 (7-C), 40.9 (4-C), 36.8 (*C*H$_2$COOMe), 35.4 (5-C), 32.0 (*C*-*gem*CH_3), 29.4 (3-*C*H_3), 26.9 (3-*C*H_3), 28.1(6-C), 23.8 (9-C), 20.8 (6-CH_3).

HRMS (ESI): *m/z* [M+Na]$^+$ calcd. for $C_{19}H_{24}NaO_5$: 355.1521; found: 355.1527.

Methyl (1,8-Dimethoxy-9*H*-xanthen-9-yl)-acetate (16).

Yield: 45%. White solid. Mp: 111.1-111.5 °C.

IR (film): 2999 (ArCH), 2945 (CH alkane), 2837 (OCH_3), 1736 (C=O ester), 1620 (C=C), 1269 (C-O), 1238 (CH_3) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.17 (t, *J* = 8.1 Hz, 2H, 3-ArH, 6-ArH), 6.71 (d, *J* = 8.1 Hz, 2H, 4-ArH, 5-ArH), 6.58 (d, *J* = 8.1 Hz, 2H, 2-ArH, 7-ArH), 4.80 (t, *J* = 5.2 Hz, 1H, 9-H), 3.87 (s, 6H, 1-ArOCH_3, 8-ArOCH_3), 3.47 (s, 3H, OCH_3), 2.79 (d, *J* = 5.2 Hz, 2H, C*H*$_2$CO$_2$CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.2 (*C*O$_2$CH$_3$), 157.1 (1-C, 8-C), 153.2 (4a-C, 4b-C), 127.9 (3-C, 6-C), 112.5 (8a-C, 9a-C), 109.0 (4-C, 5-C), 104.5 (2-C, 7-C), 55.6 (ArOCH_3), 51.2 (OCH_3), 40.0 (*C*H$_2$CO$_2$Me), 26.0 (9-C).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{18}H_{18}NaO_5$: 337.10464; found: 337.10461.

Methyl (1,8-Dimethoxy-3,6-dimethyl-9*H*-xanthen-9-yl)-acetate (17).

Yield: 20%. Hex:EtOAc 88 : 12. Yellow oil.

IR (film): 2949 (CH), 1732 (C=O ester), 1631, 1616 (C=C), 1574, 1462, 1219, 1153, 1099 (C-O), 822 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.53 (s, 2H, 4-H, 5-H), 6.39 (s, 2H, 2-H, 7-H), 4.69 (t, *J* = 5.1 Hz, 1H, 9-H), 3.84 (s, 6H, ArOCH_3), 3.48 (s, 3H, OCH_3 ester), 2.74 (d, *J* = 5.2 Hz, 2H, C*H*$_2$CO$_2$CH$_3$), 2.32 (s, 6H, 3-CH_3, 6-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.3 (C=O), 156.9 (1-C, 8-C), 153.0 (4a,4b-C), 138.0 (3-C, 6-C), 109.6 (8a-C, 9a-C), 109.4 (4-C, 5-C), 105.5 (2-C, 7-C), 55.5 (ArOMe), 51.2 (O*C*H$_3$), 40.3 (*C*H$_2$CO$_2$CH$_3$), 25.8 (9-C), 21.7 (3-CH_3, 6-CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{20}H_{22}NaO_5$: 365.13594; found: 365.13621.

Ethyl (1,8-Diethoxy-3,6-dimethyl-9*H*-xanthen-9-yl)-acetate (18).

Yield: 23%. Hex:EtOAc 94 : 6. Colourless oil.

IR (film): 2926 (CH), 1732 (C=O), 1605 (C=C), 1576, 1157, 1114, 1096, 1035, 812 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.48 (s, 2H, 4-Ar-H, 5-Ar-H), 6.37 (s, 2H, 2-H, 7-H), 4.66 (t, *J* = 4.6 Hz, 1H, 9-H), 4.06 (m, 2H, OC*H*$_2$CH$_3$), 3.89 (q, 2H, OC*H*$_2$CH$_3$ ester), 2.83 (d, *J* = 4.6 Hz, 2H, C*H*$_2$CO$_2$CH$_2$CH$_3$), 2.29 (s, 6H, 3-H, 6-H), 1.45 (t, *J* = 6.9 Hz, 6H, OCH$_2$C*H*$_3$ ester), 1.01 (m, 3H, OCH$_2$C*H*$_3$).

^{13}C NMR ($CDCl_3$): δ = 172.0 (C=O ester), 156.3 (1-C, 8-C), 152.9 (4a-C, 4b-C), 137.7 (3-C, 6-C), 109.5 (8a-C, 9a-C), 109.1 (4-C, 5-C), 106.3 (2-C, 7-C), 63.6 (O*C*H$_2$CH$_3$ ester), 59.8 (O*C*H$_2$CH$_3$), 39.7 (C*H*$_2$CO$_2$CH$_3$), 25.8 (9-C), 21.7 (Ar-CH_3), 14.7 (OCH$_2$C*H*$_3$ ester), 14.3 (OCH$_2$*CH*$_3$).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{23}H_{28}NaO_5$: 407.18290; found: 407.18277.

Note: Because of the presence of stereomers in compound **18**, a greater number of peaks in the ^{13}C NMR spectra it was observed. However, the data as presented are still useful for structure determination.

Methyl (1,8-Dimethoxy-2,3,6,7-tetramethyl-9*H*-xanthen-9-yl)-acetate (19).

Yield: 20%. Hex: EtOAc 92: 8. White solid, Mp: 117.4-118.1 °C,

IR (film): 2916 (CH), 1732 (C=O ester), 1632 (C=C), 1578, 1501, 1464, 1408, 1325, 1275, 1200, 1115 (C-O), 908, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.42 (s, 2H, 4-H, 5-H), 4.81 (t, *J* = 5.8 Hz, 1H, 9-H), 3.82 (s, 6H, ArOCH_3), 3.51 (s, 3H, OCH_3 ester), 2.63 (d, , *J* = 5.8 Hz, 2H C*H*$_2$CO$_2$CH$_3$), 2.28 (s, 6H, 3-CH_3, 6-CH_3), 2.26 (s, 6H, 2-CH_3, 7-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.4 (C=O), 154.2 (4a-C, 4b-C), 151.3 (1-C, 8-C), 135.9 (2-C, 7-C), 116.2 (3-C, 6-C), 110.2 (8a-C, 9a-C), 106.0 (4-C, 5-C), 55.4 (ArOMe), 51.2 (O*C*H$_3$), 41.2 (*C*H$_2$CO$_2$CH$_3$), 26.4 (9-C), 20.3 (3,6-CH_3), 11.3 (2,7-CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{22}H_{26}NaO_5$: 393.16725; found: 393.16696.

Ethyl (1,8-Diethoxy-2,3,6,7-tetramethyl-9*H*-xanthen-9-yl)-acetate (20).

Yield: 25%. White solid. Mp: 134.5-134.9 °C,

IR (film): 2924 (CH), 1710 (C=O), 1634 (C=C), 1574, 1501, 1412, 1325 (CH methyl), 1273, 1202, 1123, 1034, 821 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.40 (s, 2H, 4-H, 5-H), 4.77 (t, *J* = 5.1 Hz, 1H, 9-H), 4.05 (m, 4H, 1-ArOC*H*$_2$CH$_3$, 8-ArOC*H*$_2$CH$_3$), 3.86 (q, *J* = 7.0 Hz, 2H, OC*H*$_2$CH$_3$, ester), 2.76 (d, *J* = 5.1 Hz, 2H, C*H*$_2$CO$_2$CH$_2$CH$_3$), 2.26, 2.24 (2s, 6H and 6H, 2, 3, 6, 7-ArCH_3), 1.44 (t, *J* = 6.9 Hz, 6H, 1,8-ArOCH$_2$C*H*$_3$), 1.02 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.3 (C=O ester), 153.6 (4a-C, 4b-C), 151.2 (1-C, 8-C), 135.6 (2-C, 7-C), 115.7 (3-C, 6-C), 110.1 (8a-C, 9a-C), 106.9 (4-C, 5-C), 63.6 ($ArOCH_2CH_3$), 59.8 ($CO_2CH_2CH_3$), 40.6 (CH_2CO_2Et), 26.4 (9-C), 20.3 (3,6-CH_3), 14.9 ($ArOCH_2CH_3$), 13.7 ($CO_2CH_2CH_3$), 11.3 (2,7-CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{25}H_{32}NaO_5$: 435.21420; found: 435.21399.

Methyl (1,8-Dimethoxy-2,3-dimethyl-9H-xanthen-9-yl)-acetate (21).

Yield: 15 %. Colourless oil.

IR (film): 2951 (CH Ar), 2922 (CH), 2850 (CH aliphatic), 1736 (C=O ester), 1625 (C=C), 1575, 1097 cm^{-1}.

^{1}H NMR (300 MHz, CDCl3, 25°C, TMS): δ = 7.15 (t, *J* = 8.2 Hz, 1H, 6-H), 6.75 (d, *J* = 8.1 Hz, 1H, 5-H), 6.57 (d, *J* = 8.2 Hz, 1H, 7-H), 6.42 (s, 1H, 4-H), 4.80 (t, *J* = 5.5 Hz, 1H, 9-H), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3, ester), 2.71 (d, *J* = 5.6 Hz, 2H, $CH_2CO_2CH_3$), 2.27 (s, 3H, 3-CH_3), 2.22 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, CDCl3, 25°C, TMS): δ = 172.2 (C=O ester), 157.1 (8-C), 154.2 (4a-C), 153.6 (4b-C), 150.8 (1-C), 136.2 (2-C), 127.7 (6-Ar), 116.0 (3-C), 112.8 (8a-C), 109.2 (5-Ar), 104.3 (7-C), 112.8 (9a-Ar), 55.6 (OCH_3), 55.4 (OCH_3), 51.2 ($COOCH_3$), 40.6 ($CH_2CO_2CH_3$), 26.2 (9-C), 20.4 (3-CH_3), 11.2 (2-CH_3).

HRMS (ESI): *m/z* [M+ H]$^+$ calcd. for $C_{20}H_{23}O_5$: 343.15400; found: 343.15335.

Methyl (1,8-Dimethoxy-3-methyl-9*H*-xanthen-9-yl)-acetate (22):

Yield: 11 %. Yellow oil.

IR (film): 2953 (CH Ar), 2918 (CH), 2849 (CH aliphatic), 1734 (C=O ester), 1605(C=C), 1586, 1263, 1085 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.15 (t, *J* = 8.3 Hz, 1H, 6-H), 6.70 (d, *J* = 8.3 Hz, 1H, 5-H), 6.58 (d, *J* = 8.3Hz, 1H, 7-H), 6.54 (s, 1H, 4-H), 6.40 (s, 1H, 2-H), 4.74 (t, *J* = 5.1 Hz, 1H, 9-H), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3, ester), 2.76 (d, *J* = 5.2 Hz, 2H, $CH_2CO_2CH_3$), 2.32 (s, 3H, 3-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.2 (C=O ester), 157.1 (1-C), 156.8 (8-C), 153.3 (4b-C), 152.8 (4a-C), 138.1 (3-C), 127.7 (6-C), 116.0 (3-C), 112.8 (8a-C), 109.2 (5-Ar), 104.3 (7-C), 112.8 (9a-Ar), 55.6 (OCH_3), 55.4 (OCH_3), 51.2 ($COOCH_3$), 40.6 ($CH_2CO_2CH_3$), 25.9 (9-C), 21.7 (3-CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{19}H_{20}NaO_5$: 351.1207; found: 351.1208.

Methyl (1,8-Dimethoxy-2,3,6-trimethyl-9*H*-xanthen-9-yl)-acetate (23):

Yield: 15 %. Pale yellow oil.

IR (film): 2957 (CH Ar), 2929 (CH), 2849 (CH aliphatic), 1734 (C=O ester), 1630(C=C), 1387 (CH methyl), 1111 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.59 (s, 1H, 5-H), 6.41 (s, 1H, 4-H), 6.31 (s, 1H, 7-H), 4.75 (t, *J* = 5.5 Hz, 1H, 9-H), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.48(s, 3H, OCH_3, ester), 2.68 (d, *J* = 5.6 Hz, 2H, $CH_2CO_2CH_3$), 2.32 (s, 3H, 6-CH_3), 2.26 (s, 3H, 3-CH_3), 2.20 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.3 (C=O ester), 156.8, 154.2 (1-C) (8-C), 153.3, 151.0 (4a-C), (4b-C), 137.0 (6-Ar), 136.0 (2-Ar), 116.0 (3-Ar), 119.9 (8a-C), 109.5 (5-Ar), 105.5 (7-Ar), 110.5 (9a-Ar), 55.5 (OCH_3), 55.4 (OCH_3), 51.2 ($COOCH_3$), 40.7 ($CH_2CO_2CH_3$), 26.1 (9-C), 21.7 (6-CH_3), 20.4 (3-CH_3), 11.2 (2-CH_3)

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{21}H_{24}NaO_5$: 379.1516; found: 379.1512.

Methyl (8-methoxy-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl) acetate (24).

Yield: 30 %. Yellow oil.

IR (film): 2949, 2839 (CH), 1736 (C=O, ester), 1645 (C=O), 1616 (C=C), 1587, 1387 (CH methyl), 1267, 1240, 1184, 1080 (C-O), 1003, 783 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.15 (t, *J* = 8.3 Hz, 1H, 6-Ar-H), 6.65 (d, *J* = 8.1 Hz, 1H, 5-Ar-H), 6.63 (d, *J* = 8.1 Hz, 1H, 7-Ar-H), 4.37 (t, *J* = 4.6 Hz, 1H, 9-H), 3.84 (s, 3H, Ar-OCH_3), 3.49 (s, 3H, OCH_3), 2.73 (d, *J* = 4.8 Hz, 2H, $CH_2CO_2CH_3$), 2.63-2.31 (m, 4H, 2-H, 4-H), 2.05 (m, 2H, 3-H).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.4 (C=O), 172.2 (C(O) ester), 168.2 (4a-C), 157.2 (8-Ar), 151.4 (4b-Ar), 128.0 (6-Ar), 112.7, 112.6 (8a-Ar, 9a-C), 108.7 (5-C), 106.2 (7-C), 55.6 ($ArOCH_3$), 51.2 (OCH_3), 38.4 ($CH_2CO_2CH_3$), 37.0 (2-C), 27.8 (4-C), 24.7 (9-C), 20.6 (3-C).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{17}H_{18}NaO_5$: 325.10464; found: 325.10410.

Ethyl (8-ethoxy-3,6-dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (25).

Yield: 65%. Hex: EtOAc 95: 5. Yellow oil.

IR (film): 2980, 2931 (CH), 1734, 1732 (C=O), 1672 (C=C), 1574, 1371 (CH of methyl), 1288, 1178, 112, 1031, 814 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.88 (s, 1H, 7-Ar-H), 6.42 (s, 1H, 5-Ar-H), 4.34 (s, 2H, $CH_2CO_2CH_2CH_3$), 4.20-3.94 (m, 4H, $CH_2CO_2CH_2CH_3$, OCH_2CH_3), 3.01 (dd, *J* = 16.5, 6.4 Hz, 1H, 2-H), 2.96 (dd, *J* = 16.5, 7.2 Hz, 1H, 2-H), 2.67 (t, *J* = 5.2 Hz, 1H, $CHCH_2CO_2CH_2CH_3$), 2.51-2.38 (m, 1H, 4-H), 2.40 (s, 3H, 6-CH_3), 2.35-2.20 (m, 2H, 3-H, 4-H), 1.40 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 1,24 (t, 3H, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.06 (d, *J* = 6.7 Hz, 3H, 3-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 192.4 (C=O, ketone), 172.4 (C=O, ester), 155.5 (8-C), 155.1 (4b-C), 147.4 (4a-C), 140.4 (6-C), 121.3 (9a-C), 116.4 (8a-C), 105.9 (5-C), 104.8 (7-C), 63.7 (OCH_2CH_3), 60.7 ($C(O)OCH_2CH_3$), 45.8 (2-C), 41.3 (4-C), 31.0 ($CH_2C(O)OCH_2CH_3$), 29.7 (9-C), 26.5 (3-C), 22.5 (6-CH_3), 20.1 (3-CH_3), 14.6 (OCH_2CH_3), 14.2 ($C(O)OCH_2CH_3$).

HRM (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{21}H_{26}NaO_5$: 381.16725; found: 381.16667.

Methyl (8-methoxy-3,3,6,7-tetramethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (26).

Yield: 64%. Hex:EtOAc 86: 14. Yellow oil.

IR (film): 2951 (CH), 1738 (C=O ester), 1651(C=O ketone), 1582, 1499, 1466, 1385, 1286, 1194, 1105 (C-O), 822 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.46 (s, 1H, 5-H), 4.33 (t, *J* = 4.8 Hz, 1H, 9-H), 3.79 (s, 3H, $ArOCH_3$), 3.47 (s, 3H, OCH_3 ester), 2.72 (m, 2H, $CH_2CO_2CH_3$), 2.48 (d, *J* = 7.4 Hz, 2H, 4-H), 2.30 (s, 2H, 2-H), 2.25 (s, 3H, 6-Ar-CH_3), 2.13 (s, 3H, 7-Ar-CH_3), 1.14 (s, 3H, 3-CH_3), 1.11 (s, 3H, 3-CH_3).

^{13}C RMN (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.3 (C=O ketone), 172.4 (C=O ester), 166.8 (4a-C), 154.4 (4b-C), 149.2 (8-C), 136.5 (7-C), 115.8 (6-C), 111.4 (9a-C), 109.8 (8a-C), 107.8 (5-C), 55.5 (ArOMe), 51.2 (OCH_3), 50.9 (2-C), 41.6 (4-C), 38.6 ($CH_2CO_2CH_3$), 32.0 (3-C), 29.6, 27.0 (3-*gem*CH_3), 24.9 (9-C), 20.3 (6-CH_3), 11.1 (7-CH_3).

HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{21}H_{27}O_5$: 359.18530; found: 359.18409.

Ethyl (8-ethoxy-3,3,6,7-tetramethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (27).

Yield: 52 %. Pale yellow oil.

IR (film): 2951 (CH Ar), 2926 (CH), 2849 (CH aliphatic), 1734 (C=O ester), 1653 (C=O), 1558, 1387 (CH methyl), 1099, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.44 (s, 1H, 5-Ar-H), 4.32 (t, *J* = 4.5 Hz, 1H, 9-H), 4.01 (dd, *J* = 2.5, 7.0 Hz, 2H, OCH_2CH_3), 3.89 (dd, *J* = 2.7, 7.0 Hz, 2H, OCH_2CH_3, ester), 2.78 (dd, *J* = 4.5, 6.0 Hz, 2H, $CH_2CO_2CH_2CH_3$), 2.48 (d, *J* = 4.5 Hz, 2H,4-H), 2.31 (s, 2H, 2-H), 2.23 (s, 3H, 6-CH_3), 2.11 (s, 3H, 7-CH_3), 1.41 (t, 3H, *J* = 7.0 Hz, $ArOCH_2CH_3$), 1.15(s, 3H, 3-CH_3), 1.11 (s, 3H, 3-CH_3), 1.04 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.4 (C=O), 172.2 (C=O ester), 166.7 (4a-C), 153.8 (4b-C), 149.2 (8-C), 136.3 (7-Ar), 115.5 (6-Ar), 111.4 (9a-C), 109.7 (8a-C), 108.5 (5-Ar), 63.7 ($ArOCH_2CH_3$), 59.8 ($COOCH_2CH_3$), 51.0 (2-C), 41.6 (4-C), 38.4 (CH_2CO_2Et), 32.0 (3-C), 29.6, 27.1 (3-*gem*CH_3), 25.0 (9-C), 20.3 (6-CH_3), 14.9 ($ArOCH_2CH_3$), 13.9 (CH_2CH_3), 11.1 (7-CH_3).

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{23}H_{30}NaO_5$: 409.19855; found: 409.19824.

Methyl (8-methoxy-3,3-dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (28).

Yield: 35 %. Colourless oil.

IR (film): 2951 (CH Ar), 2926 (CH), 2849 (CH aliphatic), 1736 (C=O ester), 1647(C=O), 1583, 1387 (CH methyl), 1267, 1080, 1029 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.15 (t, *J* = 8.2 Hz, 1H, 6-H), 6.64 (d, *J* = 8.2 Hz, 1H, 5-H), 6.63 (d, *J* = 8.2 Hz, 1H, 7-H), 4.34 (t, *J* = 4.4 Hz, 1H, 9-H), 3.84 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3, ester), 2.77 (d, *J* = 4.6 Hz, 2H, $CH_2CO_2CH_3$), 2.46 (s, 2H, 4-H), 2.30 (s, 2H, 2-H), 1.13 (s, 3H, 3-CH_3), 1.11 (s, 3H, 3-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.3 (C=O), 172.3 (C=O ester), 166.7 (4a-C), 157.2 (8-C), 151.5 (4b-C), 128.0 (6-Ar), 108.8 (5-Ar), 106.2 (7-Ar), 112.6 (8a-C), 111.4 (9a-Ar), 55.6 (OCH_3), 51.2 ($COOCH_3$), 50.9 (2-C), 41.5 (4-C), 38.0 ($CH_2CO_2CH_3$), 32.0 (3-C), 29.6, 26.9 (3-*gem*CH_3), 24.8 (9-C).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{23}O_5$: 331.15400; found: 331.15413.

Methyl (8-methoxy-6,7-dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (29).

Yield: 19 %. Colourless oil.

IR (film): 2956 (CH Ar), 2921 (CH), 2850 (CH aliphatic), 1735 (C=O ester), 1650 (C=O), 1387 (CH methyl), 1103 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.46 (s, 1H, 5-Ar-H), 4.36 (t, *J* = 4.9 Hz, 1H, 9-H), 3.79 (s, 3H, $ArOCH_3$), 3.50 (s, 3H, OCH_3), 2.69 (dd, *J* = 4.8 Hz, 2H, $CH_2CO_2CH_3$), 2.68-2.54 (m, 2H, 4-H), 2.48-2.38 (m, 2H, 2-H), 2.25 (s, 3H, 7-CH_3), 2.14 (s, 3H, 6-CH_3), 2.04 (m, 2H, 3-H).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.5 (C=O), 172.3 (C=O ester), 168.3 (4a-C), 154.3 (4b-C), 149.1 (8-C), 136.5 (7-Ar), 115.8 (6-C), 112.7 (9a-C), 109.9 (8a-C), 107.8 (5-C), 55.5 ($ArOCH_3$), 51.2 ($COOCH_3$), 38.9 ($CH_2CO_2CH_3$), 37.1 (2-C), 27.9 (4-C), 24.8 (9-C), 20.6 (3-C), 20.3 (6-CH_3), 11.1 (7-CH_3).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{23}O_5$: 331.15400; found: 331.15452.

Methyl (8-methoxy-2,2-dimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl) acetate (30).

Yield: 79 %. Colourless oil.

IR (film): 2955 (CH Ar), 2920 (CH), 2849 (CH aliphatic), 1732 (C=O ester), 1651 (C=O), 1590, 1387 (CH methyl), 1267, 1080 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.15 (t, *J* = 8.2 Hz, 1H, 6-H), 6.64 and 6.62 (t, *J* = 8.2 Hz, 1H, 5-H), (t, *J* = 8.2 Hz, 1H, 7-H), 4.34 (t, *J* = 4.7 Hz, 1H, 9-H), 3.84 (s, 3H, $ArOCH_3$), 3.48 (s, 3H, OCH_3), 2.69 (dd, *J* = 4.7 Hz, *J* = 1.1 Hz, 2H, $CH_2CO_2CH_3$), 2.60 (m, 2H, 4-H), 1.88 (m, 2H, 3-H), 1.17, 1.10 (2s, 3H and 3H, 2-*gem*CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 202.1 (C=O), 172.3 (C=O ester), 166.0 (4a-C), 157.2 (8-Ar), 151.4 (4b-Ar), 127.9 (6-Ar), 112.7 (8a-Ar), 110.7 (9a-C), 108.6 and 106.1(5-Ar, 7-Ar), 55.6 ($ArOCH_3$), 51.2 ($COOCH_3$), 40.4 (2-C), 38.5 ($CH_2CO_2CH_3$), 34.2 (3-C), 24.9, 24.2 (2-*gem*CH_3), 24.7 (4-C), 25.1 (9-C).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{23}O_5$: 331.15400; found: 331.15406.

Methyl (8-methoxy-6-methyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (31).

Yield: 10 %. Colourless oil.

IR (film): 2951 (CH Ar), 2918 (CH), 2849 (CH aliphatic), 1736 (C=O ester), 1645 (C=O), 1582, 1387 (CH methyl), 1092 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.47 (s, 1H, 5-H), 6.44 (s, 1H, 7-H), 4.32 (t, *J* = 4.4 Hz, 1H, 9-H), 3.82 (s, 3H, $ArOCH_3$), 3.50 (s, 3H, OCH_3), 2.71 (dd, *J* = 4.6 Hz, *J* = 1.6 Hz, 2H, $CH_2CO_2CH_3$), 2.79 (m, 4H, 2-H and 4-H), 2.31 (s, 3H, $ArCH_3$), 2.05 (m, 2H, 3-H).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.4 (C=O), 172.3 (C=O ester), 168.3 (4a-C), 156.9 (8a-Ar), 151.1 (4b-Ar), 138.3 (6-Ar), 112.7 (9a-C), 109.1 (5-Ar), 107.3 (7-Ar), 55.6 ($ArOCH_3$), 51.2 ($COOCH_3$), 38.5 (2-C), 37.0 ($CH_2CO_2CH_3$), 27.0 (4-C), 24.6 (9-C), 21.6 ($ArCH_3$), 20.6 (3-C).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{18}H_{21}O_5$: 317.3835; found: 317.13713

Methyl (8-methoxy-2,2,6,7-tetramethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (32).

Yield: 59 %. Colourless oil.

IR (film): 2947 (CH Ar), 2918 (CH), 2849 (CH aliphatic), 1734 (C=O ester), 1647 (C=O), 1541, 1387 (CH methyl), 1105 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.46 (s, 1H, 5-H), 4.33 (t, *J* = 4.8 Hz, 1H, 9-H), 3.80 (s, 3H, $ArOCH_3$), 3.49 (s, 3H, OCH_3), 2.66- 2.60 (m, 4H, 4-H and $CH_2CO_2CH_3$), 2.25 (s, 3H, 7-CH_3), 2.12 (s, 3H, 6-CH_3), 1.92- 1.83 (m, 2H, 3-H), 1.16 and 1.10 (2s, 3H and 3H, 2-*gem*CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 202.1 (C=O), 172.4 (C=O ester), 166.2 (4a-C), 149.1 (8-Ar), 154.4 (4b-Ar), 136.6 (7-Ar), 115.7(6-Ar), 110.7 (9a-C), 109.9 (8a-Ar), 107.7 (5-Ar), 55.5 ($ArOCH_3$), 51.2 ($COOCH_3$), 40.3 (2-C), 39.0 ($CH_2CO_2CH_3$), 34.3 (3-C), 24.8 (4-C), 24.9 and 24.2 (2-*gem*CH_3), 25.2 (9-C), 20.3(6-CH_3), 11.1(7-CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{21}H_{26}NaO_5$: 381.1678; found: 381.1708.

Methyl (8-methoxy-3,3,6-trimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (33).

Yield: 25 %. Colourless oil.

IR (film): 2953 (CH Ar), 2920 (CH), 2849 (CH aliphatic), 1736 (C=O ester), 1649 (C=O), 1583, 1385 (CH methyl), 1092, 1036 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.47 (s, 1H, 5-H), 6.44 (s, 1H, 7-H), 4.29 (t, *J* = 4.6 Hz, 1H, 9-H), 3.82 (s, 3H, $ArOCH_3$), 3.47 (s, 3H, OCH_3), 2.76 (dd, *J* = 4.6 Hz, *J* = 1.1 Hz, 2H, $CH_2CO_2CH_3$), 2.44 (s, 2H, 4-H), 2.31 (s, 3H, 6-CH_3), 2.29 (s, 2H, 2-H), 1.13, 1.10 (2s, 3H and 3H 3-*gem*CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.3 (C=O), 172.4 (C=O ester), 166.8 (4a-C), 157.0 (8-Ar), 151.2 (4b-Ar), 138.3 (6-Ar), 111.6 (9a-C), 109.4 (8a-Ar), 109.2 (5-Ar), 107.3(7-Ar), 55.6 ($ArOCH_3$), 51.2 ($COOCH_3$), 50.9 (2-C), 41.5 (4-C), 38.1 ($CH_2CO_2CH_3$), 32.0 (3-C), 29.6, 27.0 (3-*gem*CH_3), 24.6 (9-C), 21.6 (6-CH_3).

HRMS (ESI): *m/z* [M+ H]$^+$ calcd. for $C_{20}H_{25}O_5$: 345.16965; found: 345.16796.

Methyl (8-methoxy-3,6,7-trimethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-xanthen-9-yl)acetate (34).

Yield: 12 %. Pale yellow oil.

IR (film): 2951 (CH Ar), 2921(CH), 2849 (CH aliphatic), 1734 (C=O ester), 1660 (C=O), 1387 (CH methyl), 1092 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.90 (s, 1H, 5-H), 4.31 (t, *J* = 4.0 Hz, 1H, 9-H), 3.86 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3, ester), 3.02 (br.s, 2H, 4-H), 2.72 (dd, *J* = 4.0 Hz, 2H, $CH_2CO_2CH_3$), 2.50 (s, 2H, 2-H), 2.46 (br. s, 1H, 3-H), 2.25 (s, 3H, Ar-CH_3), 2.13 (s, 3H, Ar-CH_3), 1.15 (br.s, 3H, 3-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 193.5 (C=O), 172.5 (C=O ester), 171.0 (4a-C), 149.1 (8-C), 155.3 (4b-C), 136.7 (7-C), 116.4 (6-Ar), 115.8 (9a-Ar), 105.3 (8a-C), 105.1(5-Ar), 55.4 (OCH_3), 51.2 ($COOCH_3$), 48.7 (4-C), 45.4 (2-C), 38.1 ($CH_2CO_2CH_3$), 28.0 (3-CH_3), 24.9 (9-C), 22.6 (3-C), 20.4 (6-CH_3), 11.0 (7-CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{20}H_{24}NaO_5$: 367.1516; found: 367.1519.

Note: The acids compounds **36-38** were obtained by solid phase synthesis and described in *ref. 13*.

(2,2,5,5-Tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)-acetic acid (38).

Yield: 99%. Colourless oil.

IR (film): 3200 (O-H acid), 2965, 2968 (CH), 1713 (C=O), 1661 (O=C-C=C), 1614 (C=C), 1176 (C-O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.92 (t, *J* = 4.1 Hz, 1H, 9-H), 2.58-2.43 (m, 4H, 4-H, 7-H), 2.52 (d, *J* = 4.1 Hz, 2H, CH_2COOH), 1.87-1.79 (m, 4H, 3-H, 6-H), 1.24 (s, 3H, 5-CH_3), 1.23 (s, 3H, 5-CH_3), 1.11 (s, 3H, 2-CH_3), 1.09 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 202.6 (1-*C*), 197.9 (8-C), 177.5 (COOH), 171.5 (4b-C), 164.5 (4a-C), 112.5 (8a-C), 112.1 (9a-C), 40.5 (2-C), 38.6 (CH_2COOH), 35.2 (6-C), 34.6 (5-C), 34.0 (3-C), 33.8 (7-C), 26.1 (5-CH_3), 24.6 (2-CH_3), 24.4 (5-CH_3), 24.2 (2-CH_3), 24.0 (4-C), 23.8 (9-C).

HRMS (ESI): *m/z* [M+ 2Na]$^+$ calcd. for $C_{19}H_{24}Na_2O_5$: 377.13354; found: 377.13245.

Hydrolysis of dimethoxy aryl methyl ester. Preparation of 1,8-dimethoxy-9*H*-xanthen-9-yl)-acetic acid (39). Aqueous LiOH solution (1.0 M, 4 mL, 4 mmol) was added to a solution of methyl ester (0.21 mmol) in THF (4.0 mL). The reaction mixture was stirred at room temperature for 3 days. After removal of THF in vacuo, the residue was redissolved with EtAcO. The aqueous layers were cautiously acidified to pH = 4 with 10% HCl and extracted with EtAcO (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered and the solvent was removed under vacuum.

Yield: 99%. White solid. Mp: 188.6-189.6 °C.

IR (film): 3479 (OH), 2924 (CH), 2850 (CH aliphatic), 1705 (C=O ester), 1620, 1582 (C=CAr), 1269 (C-OAr), 1238 (CH_3-OAr) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.17 (t, *J* = 8.2 Hz, 2H, 3-Ar-H, 6-Ar-H), 6.70 (d, *J* = 8.2 Hz, 2H, 2-Ar-H, 7-Ar-H), 6.57 (d, *J* = 8.2 Hz, 2H, 4-Ar-H, 5-Ar-H), 4.83 (t, *J* = 5.5 Hz, 1H, 9-H), 3.79 (s, 6H, OCH_3), 2.76 (d, *J* = 5.5 Hz, 2H, CH_2CO_2H).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 178.2 (C=O), 157.2 (1-C, 8-C), 153.0 (4a-C, 4b-C), 128.0 (3-C, 6-C), 112.2 (8a-C, 9a-C), 109.1 (4-C, 5-C), 104.5 (2-C, 7-C), 55.4 (OCH_3), 40.6 (CH_2CO_2H), 26.1 (9-C).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{17}H_{16}NaO_5$: 323.08954; found: 323.08899.

Hydrolysis of diethoxy aryl ethyl ester. Preparation of (1,8-diethoxy-2,3,6,7-tetramethyl-9*H*-xanthen-9-yl)-acetic acid (40). Aqueous KOH solution (5.0 M, 1.6 mL, 8 mmol) was added to a solution of ethyl ester (0.24 mmol) in EtOH (4.0 mL). The reaction mixture was refluxed under stirring for 2 hours. After removal of EtOH in vacuo, the residue was redissolved with EtAcO. The aqueous layers were cautiously acidified to pH = 4 with 10% HCl and extracted with EtAcO (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulphate. After filtration and concentration, the residue was purified by silica gel column chromatography.

Yield: quantitative, White solid, Mp: 206.4 - 207.0 °C, Hex:EtOAc 90 : 10.

IR (film): 3050 (OH), 2978 (CH), 2924, 2879 (CH aliphatic), 1709 (C=O), 1633, 1576 (C=CAr), 1200 (C-OAr), 1119 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.39 (s, 2H, 4-ArH), 4.83 (t, *J* = 5.5 Hz, 1H, C*H*CH_2CO_2H), 4.01 (d quartet, *J* = 2.1, 7.1 Hz, 4H, OC*H*$_2CH_3$), 2.68 (d, *J* = 5.5 Hz, 2H, C*H*$_2CO_2H$), 2.27(s, 6H, 3,6-CH_3), 2.24 (s, 6H, 2,7-CH_3), 1.40 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 177.5 (C=O), 151.2 (1-C, 8-C), 153.6 (4a-C, 4b-C), 135.9 (2-C, 7-C), 116.7 (3-C, 6-C), 110.0 (8a-C, 9a-C), 106.8 (4-C, 5-C), 63.5 (O*C*H_2CH_3), 41.5 (*C*H_2CO_2H), 26.2 (9-C), 20.3 (3,6-CH_3), 14.7 (OCH_2*C*H_3), 11.3 (2,7-CH_3).

HRMS (ESI): *m/z* [M+ 2Na]$^+$ calcd. for $C_{23}H_{27}Na_2O_5$: 429.16484; found: 429.16355.

_N_-Benzyl-2-(1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)-acetamide (41).

Yield 71.3%. CH_2Cl_2:MeOH 94: 6. Yellow oil.

IR (film): 3190 (N-H), 2949 (CH), 1674 (C=O), 1647 (C=O amide), 1616 (C=C), 1543 (C-N), 1381 (CH_2), 1176 (C-O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.36-7.25 (m, 5H, Ar-H), 5.98 (bs, 1H, NH), 4.34 (d, 2H, *J* = 5.8 Hz, CH_2Ar), 3.89 (t, 1H, *J* = 4.4 Hz, 9-H), 2.49-2.37 (m, 8H, 2-H, 4-H, 5-H, 7-H), 2.48 (d, 2H, *J* = 4.4 Hz, C*H*$_2$C(O)NH), 2.03-1.90 (m, 4H, 3-H, 6-H).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.8 (1-C, 8-C), 171.2 (CONH), 165.9 (4a-C, 4b-C), 138.6, 128.6, 128.0, 127.3 (Ar), 114.8 (8a-C, 9a-C), 43.4 (CH_2Ar), 40.3 (*C*H_2C(O)NH), 36.9 (2-C, 7-C), 27.1 (4-C, 5-C), 23.9 (9-C), 20.3 (3-C, 6-C).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{22}H_{23}NNaO_4$: 388.15193; found: 388.15089.

_N_-Benzyl-2-(3,6-dimethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)-acetamide (42).

Yield 60 %.. Hex:EtOAc 45 : 55. White solid. Mp: 140.2-140.6 °C.

IR (film): 3440 (N-H), 2953 (CH), 1647 (C=O), 1630 (C=C), 1456 (C-N), 1382 (CH of methyl), 1190, 1132 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.27-7.25 (m, 5H, Ar-H), 6.22 (br.s, 1H, NH), 4.30 (d, *J* = 5.7 Hz, 2H, CH_2Ar), 3.83 (br.s, 1H, 9-H), 2.55-2.31 (m, 8H, 2-H, 4-H, 5-H, 7-H), 2.31-1.83 (m, 4H, 3-H, 6-H, C*H*$_2$CONH), 1.05 (d, 3H, *J* = 5.4 Hz, CH_3), 1.02 (d, 3H, *J* = 5.3 Hz, CH_3).

^{13}C NMR (75 MHz, CDCl3, 25°C, TMS): δ = 197.7 (1-C, 8-C), 171.2 (C(O)NH), 165.8 (4a-C, 4b-C), 138.7, 128.6, 128.1, 127.3 (Ar), 114.4 (8a-C, 9a-C), 45.3 (2-C, 7-C), 43.3 (CH_2Ar), 40.4 (*C*H_2CONH), 35.3 (4-C, 5-C), 28.3, 27.9 (3-C, 6-C), 24.4 (9-C), 20.7 (CH_3).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{24}H_{27}NNaO_4$: 416.18323; found: 416.18455.

_N_-Benzyl-2-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)-acetamide (43).

Yield 53 %. Hex:EtOAc 57: 43, White crystals. Mp: 195.2-195.5 °C.

IR (film): 3321 (N-H), 2959 (CH), 1673 (C=O), 1662 (C=O amide), 1620 (C=C), 1539 (C-N), 1380 (C-N, *gem*CH_3) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.31-7.21 (m, 5H, Ar-H), 5.82 (bs, 1H, NH), 4.30 (d, *J* = 5.7 Hz, 2H, CH_2Ar), 3.85 (t, *J* = 3.9 Hz, 1H, 9-H), 2.57 (d, *J* = 4.3 Hz, 2H, C*H*$_2$C(O)NH), 2.37 (d, *J* = 17.7 Hz, 4H, 2-H, 7-H), 2.24 (d, *J* = 17.7 Hz, 4H, 4-H, 5-H), 1.11 (s, 6H, CH_3), 1.09 (s, 6H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.7 (1-C, 8-C), 171.2 (C(O)NH), 164.6 (4a-C, 4b-C), 138.4, 128.6, 128.0, 127.4 (Ar), 113.5 (8a-C, 9a-C), 50.8 (2-C, 7-C), 43.4 (CH_2Ar), 40.8 (4-C, 5-C), 38.9 (*C*H_2C(O)NH), 32.1 (3-C, 6-C), 29.1 (CH_3), 27.3 (CH_3), 24.3 (9-C).

HRMS (ESI): *m/z* [M+ K]$^+$ calcd. for $C_{26}H_{31}KNO_4$: 460.18847; found: 460.18708.

_N_-Benzyl-2-(2,2,5,5-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)-acetamide (44).

Yield 54 %. Hex: EtOAc 62: 38. Yellow oil.

IR (film): 3341 (N-H), 2963, 2926 (CH), 1674, 1645 (C=O amide, C=O ketone, Ar), 1620 (C=C), 1381 (C-N), 1175 (C-O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.33-7.24 (m, 5H, Ar-H), 5.95 (bs, 1H, NH), 4.40 (dd, *J* = 15.0, 6.0 Hz, 1H, CH_2Ar), 4.26 (dd, *J* = 15.0, 6.0 Hz, 1H, CH_2Ar), 3.87 (t, *J* = 4.1 Hz, 1H, 9-H), 2.57-2.40 (m, 6H, C*H*$_2$C(O)NH, 4-H, 7-H), 1.89-1.76 (m, 4H, 3-H, 6-H), 1.30 (s, 3H, 5-CH_3), 1.22 (s, 3H, 5-CH_3), 1.10 (s, 3H, 2-CH_3), 1.08 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 202.4 (1-C), 197.5 (8-C), 171.0 (C(O)NH), 170.8 (4b-C), 164.1 (4a-C), 138.5, 128.6, 127.9, 127.4 (Ar), 113.1, 112.7 (8a-C, 9a-C), 43.5 (CH_2Ar), 40.7 (*C*H_2C(O)NH), 40.5 (2-C), 33.8 (7-C), 35.3 and 34.0 (3-C, 6-C), 34.5 (5-C), 26.2 (5-CH_3), 24.7 (2-CH_3), 24.5 (9-C), 24.4 (5-CH_3), 24.2 (2-CH_3), 24.0 (4-C).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{26}H_{31}NNaO_4$: 444.21453; found: 444.21390.

_N_-(3-Dimethylamino-propyl)-2-(1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-9-yl)-acetamide (45).

Yield 99 %. MeOH:NH_3 95: 5. Yellow oil.

IR (film): 3363 (N-H), 2947 (CH), 1658 (C=O), 1651 (C=O amide), 1554 (C-N), 1265 (C-N) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.85 (br.s, 1H, NH), 3.85 (t, *J* = 4.6 Hz, 1H, 9-H), 3.21 (q, *J*= 6.2 Hz, 2H, NHC*H*$_2$), 2.63-2.27 (m, 12H, 2-H, 4-H, 5-H, 7-H, C*H*$_2$CONH, C*H*$_2$N$(CH_3)_2$), 2.34 (s, 6H, N$(CH_3)_2$), 2.07-1.99 (m, 4H, 3-H, 6-H), 1.70 (m, 2H, C*H*$_2$$CH_2N(CH_3)_2$).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.6 (1-C, 8-C), 171.5 (CONH), 165.8 (4a-C, 4b-C), 115.2 (8a-C, 9a-C), 57.3 (*C*H_2N$(CH_3)_2$), 44.7 (N$(CH_3)_2$), 41.2 (NHCH_2), 38.0 (*C*H_2CONH), 36.9 (2-C, 7-C), 27.2 (4-C, 5-C), 26.2 (*C*$H_2$$CH_2N(CH_3)_2$), 24.1 (9-C), 20.4 (3-C, 6-C).

HRMS (ESI): *m/z* [M+ Na]$^+$ calcd. for $C_{20}H_{28}N_2NaO_4$: 383.19413; found: 383.19337.

_N_-(3-Dimethylamino-propyl)-2-(3,6-dimethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-*1H*-xanthen-9-yl)-acetamide (46).

Yield: 68%. CH_2Cl_2: MeOH 75: 25. Pale yellow oil.

IR (film): 3381 (N-H), 2953 (CH), 1645 (C=O), 1614 (C=C), 1450 (C-N), 1385 (CH methyl), 1190, 1099, 744 cm^{-1}.

^{1}H NMR (D_2O, 300 MHz): δ = 3.42 (t, *J* = 4.5 Hz, 1H, 9-H), 2.92 (t, *J* = 7 Hz, 2H, $NHCH_2$), 2.76 (t, *J* = 7 Hz, 2H, $CH_2N(CH_3)_2$), 2.56 (s, 6H, N-CH_3),

2.40-2.25 (m, 6H, 4-H, 5-H, $CH_2C(O)NH$), 2.25-2.00 (m, 6H, 2-H, 3-H, 6-H, 7-H), 1.62 (m, 2H, $CH_2CH_2N(CH_3)_2$), 1.02-0.89 (m, 6H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 201.7 (1-C, 8-C), 173.5 (C(O)NH), 168.7 (4a-C, 4b-C), 113.5 (8a-C, 9a-C), 55.3 (CH_2N-*gem*CH_3), 42.9 (N-*gem*CH_3), 39.6 ($CH_2C(O)NH$), 38.5 (2-C, 7-C), 36.3 ($C(O)NHCH_2$), 34.4 (4-C, 5-C), 27.4 (3-C, 6-C), 24.4 ($CH_2CH_2CH_2NMe_2$), 23.5 (9-C), 21.5 (CH_3), 19.7 (CH_3).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{33}N_2O_4$: 389.24348; found: 389.24296.

_N_-(3-Dimethylamino-propyl)-2-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1_H_-xanthen-9-yl)-acetamide (47).

Yield: 88.2%. CH_2Cl_2:MeOH 80: 20. Colourless oil.

IR (film): 3357 (N-H), 2956 (CH), 1661 (C=O), 1654 (C=O amide), 1620 (C=C), 1382 (C-N), 1380 (*gem*CH_3) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.68 (br.s, 1H, NH), 3.82 (t, *J* = 3.8 Hz, 1H, 9-H), 3.17 (q, *J*= 6.4 Hz, 2H, $NHCH_2$), 2.48 (d, *J*= 4.3 Hz, 2H, CH_2CONH), 2.30 (t, *J*= 6.4 Hz, 2H, $CH_2N(CH_3)_2$), 2.20 (s, 6H, $N(CH_3)_2$), 2.38 (s, 4H, 2-H, 7-H), 2.28 (s, 4H, 4-H, 5-H), 1.57 (m, 2H, $CH_2CH_2N(CH_3)_2$), 1.12 and 1.09 (2s, 12H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 197.6 (1-C, 8-C), 171.4 (C(O)NH), 164.6 (4a-C, 4b-C), 113.7 (8a-C, 9a-C), 58.3 ($CH_2N(CH_3)_2$), 51.0 (2-C, 7-C), 45.4 ($N(CH_3)_2$), 40.9 (4-C, 5-C), 39.0 ($NHCH_2$), 38.9 (CH_2CONH), 32.1 (*C*-*gem*CH_3), 29.4 (CH_3), 27.1 (CH_3), 26.3 ($CH_2CH_2N(CH_3)_2$), 24.2 (9-C).

HRMS (ESI): *m/z* $[M+Na]^+$ calcd. for $C_{24}H_{36}N_2NaO_4$: 439.25673; found: 439.25571.

_N_-(3-Dimethylamino-propyl)-2-(2,2,5,5-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1_H_-xanthen-9-yl)-acetamide (48).

Yield 58%. CH_2Cl_2:MeOH 40: 60. Yellow oil.

IR (film): 3362 (N-H), 2963 (CH), 1651 (C=O), 1665 (C=O amide), 1614 (C=C), 1379 (C-N), 1174 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.58 (br.s, 1H, NH), 3.85 (t, *J* = 4.6 Hz, 1H, 9-H), 3.19 (ddd, *J* = 13.5, 6.4, 3.0 Hz, 2H, $NHCH_2$), 2.54 (m, 2H, $CH_2N(CH_3)_2$), 2.45 (t, *J*= 6.4 Hz, 2H, 7-H), 2.33-2.28 (m, 4H, 4-H, $CH_2C(O)NH$), 2.19 (s, 6H, $N(CH_3)_2$), 1.94-1.78 (m, 4H, 3-H, 6-H), 1.60 (q, *J*= 6.7 Hz, 2H, $CH_2CH_2N(CH_3)_2$), 1.29 (s, 3H, 5-CH_3), 1.22 (s, 3H, 5-CH_3), 1.15 (s, 3H, 2-CH_3), 1.09 (s, 3H, 2-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 202.3 (1-C), 196.8 (8-C), 171.1 (C(O)NH), 170.9 (4b-C), 163.9 (4a-*C*), 113.1 and 113.0 (8a-C, 9a-C), 58.1 ($CH_2N(CH_3)_2$), 45.4 ($N(CH_3)_2$), 40.8 ($CH_2C(O)NH$), 40.5 (2-C), 38.4 ($NHCH_2$), 35.4 (6-C), 34.5 (5-C), 34.1 (3-C), 33.8 (7-C), 26.7 ($CH_2CH_2N(CH_3)_2$), 26.3 (5-CH_3), 24.7 (2-CH_3), 24.4 (9-C), 24.4 (5-CH_3), 24.2 (2-CH_3), 24.0 (4-C).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{24}H_{37}N_2O_4$: 417.27478; found: 417.27359.

2-(1,8-Dimethoxy-9H-xanthen-9-yl)-_N_-(3-dimethylamino-propyl)-acetamide (49).

Yield: 60 %. CH_2Cl_2: MeOH 88: 12. Colourless oil.

IR (film) 3300 (N-H), 2934 (CH), 2837 (OMe), 1651 (C=O amide), 1620 (C=CAr), 1456 (Ar), 1289 ($ArOCH_3$), 1094 (C-N-C), 1082 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.15 (t, *J* = 8.3 Hz, 2H, 3-ArH, 6-ArH), 6.69 (d, *J* = 8.0 Hz, 2H, 2-ArH, 7-ArH), 6.59 (d, *J* = 8.0 Hz, 2H, 4-ArH, 5-ArH), 5.89 (br,s, 1H, NH), 4.81 (t, *J* = 5.4 Hz, 1H, 9-H), 3.87 (s, 6H, OCH_3), 3.10 (m, 2H, $CH_2NHC(O)$), 2.58 (d, 2H, CH_2CONH), 2.23 (m, 2H, $CH_2N(CH_3)_2$), 2.19 (s, 6H, $N(CH_3)_2$), 1.48 (m, 2H, $CH_2CH_2NHC(O)$).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 171.0 (C(O)NH), 157.1 (1-C, 8-C), 153.1 (4a-C, 4b-C), 127.9 (3-C, 6-C), 113.1 (8a-C, 9a-C), 109.1 (4-*C*, 5-C), 104.7 (2-C, 7-C), 57.5 ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 45.1 ($(CH_3)_2N$-), 43.3 ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 38.2 ($CH_2C(O)N$), 26.6 ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 26.4 (9-C).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{29}N_2O_4$: 385.21088; found: 385.21218

2-(1,8-Diethoxy-2,3,6,7-tetramethyl-9_H_-xanthen-9-yl)-_N_-(3-dimethylamino-propyl)-acetamide (50).

Yield: 51 %. CH_2Cl_2:MeOH 96: 4. Colourless oil.

IR (film): 3340 (N-H), 2972 (=CH), 2926 (CH), 2874, 1633 (C=O amide), 1575 (C=CAr), 1506, 1450 (Ar), 1202 (C-O-CAr), 1168, 1107 (C-N-C) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 6.43 (s, 1H, 4-Ar-H), 5.90 (t, *J* = 6.0 Hz, 1H, NH), 4.74 (t, *J* = 5.1, 1H, 9-H), 4.08 (ABX_3 system, J_{AB} = 14.2, J_{AX} = J_{BX} = 7.1 Hz, 2H, OCH_2CH_3), 3.10 (q, *J* = 6.4 Hz, 2H, ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O)), 2.67 (d, *J* = 5.1 Hz, 2H, CH_2CONH), 2.61 (t, 2H, *J* = 7.1 Hz, $(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 2.56 (s, 3H, $(CH_3)_2N$-), 2.26 (s, 6H, 3-CH_3, 6-CH_3), 2.22 (s, 6H, 2-CH_3, 7-CH_3), 1.79 (p, *J* = 7.2 Hz, 2H, $(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 1.45 (t, 6H, *J* = 7.0 Hz, OCH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 172.4 (C(O)NH), 153.6 (4a-C, 4b-C), 151.2 (1-Ar), 136.0 (3-Ar), 115.8 (2-Ar), 110.2 (9a-C), 107.3 (4-C), 63.8 (OCH_2CH_3), 55.5 ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 43.2 ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 42.4 (CH_2CONH), 36.3 ($(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 26.9 (9-C), 25.3 $(CH_3)_2NCH_2CH_2CH_2NH$-C=O), 20.3 (3-CH_3, 6-CH_3), 11.4 (2-CH_3, 7-CH_3).

HRMS (ESI): *m/z* $[M+H]^+$ calcd. for $C_{28}H_{41}N_2O_4$: 469.30608; found: 469.30440.

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