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New chiral derivatives of xanthones: Synthesis and investigation of enantioselectivity as inhibitors of growth of human tumor cell lines

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ABSTRACT

A highly efficient and practical methodology for synthesis of new chiral derivatives of xanthones (CDXs) in enantiomerically pure form has been developed. According to this approach, thirty CDXs (**3**–**32**) were synthesized by coupling a carboxyxanthone (**1**) and a carboxymethoxyxanthone (**2**) with both enantiomers of commercially available chiral building blocks, namely six amino alcohols, one amine and one amino ester. The activation of the carboxylic acid group of the xanthonic scaffold was carried out with the coupling reagent *O*-(benzotriazol-1-yl)-*N*-*N*-*N*′-*N*′-tetramethyluronium tetrafluoroborate (TBTU), in the presence of a catalytic amount of TEA in anhydrous THF. The coupling reactions with the chiral blocks were performed at room temperature with short reactions times, excellent yields (ranging from 94% to 99%), and very high enantiomeric excess. The synthesized CDXs were evaluated for their effect on the *in vitro* growth of three human tumor cell lines, namely A375-C5 (melanoma), MCF-7 (breast adenocarcinoma), and NCI-H460 (non-small cell lung cancer). The most active compound was CDX **15** being active in all human tumor cell lines with values of GI_{50} of 32.15 ± 2.03 μM for A375-C5, 22.55 ± 1.99 μM for MCF-7, and 14.05 ± 1.82 μM for NCI-H460. Nevertheless, some CDXs showed cell-type selectivity. Furthermore, the growth inhibitory effects, in some cases, demonstrated to be depending on the stereochemistry of the CDXs. An interesting example was observed with the enantiomers **3** and **4**, which demonstrated high enantioselectivity for MCF-7 and NCI-H460 cell lines. It can be inferred that the effects on the growth of the human tumor cell lines can be ascribed not only to the nature and positions of substituents on the xanthonic scaffold but also to the stereochemistry of the CDXs. Some considerations regarding structure–activity relationship within this class of compounds will be highlighted.

1. Introduction

The number of enantiomerically pure drugs in the pharmaceutical market has been increasing.[1] The different biological/pharmacological activities of enantiomers, together with the advances in synthetic and analytical methodologies as well as the regulatory requirements gave a great contribution to the considerable increased interest in this field. The gains in potency, efficacy, safety and selectivity obtained by treatment with single enantiomers rather than racemates are undeniable.[2] The enantiomerically pure drugs can be obtained either by preparative resolution of a cracemate or by enantioselective synthesis of the desired enantiomer. Regarding the early steps of drug development, the HPLC chromatographic resolution of a racemate using chiral stationary phases (CSPs) is the preferential approach since it can provide both enantiomers with high enantiomeric excess (ee).[3] Concerning enantioselective synthesis, it can be useful when a large amount

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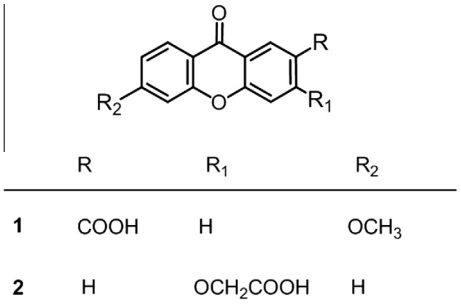


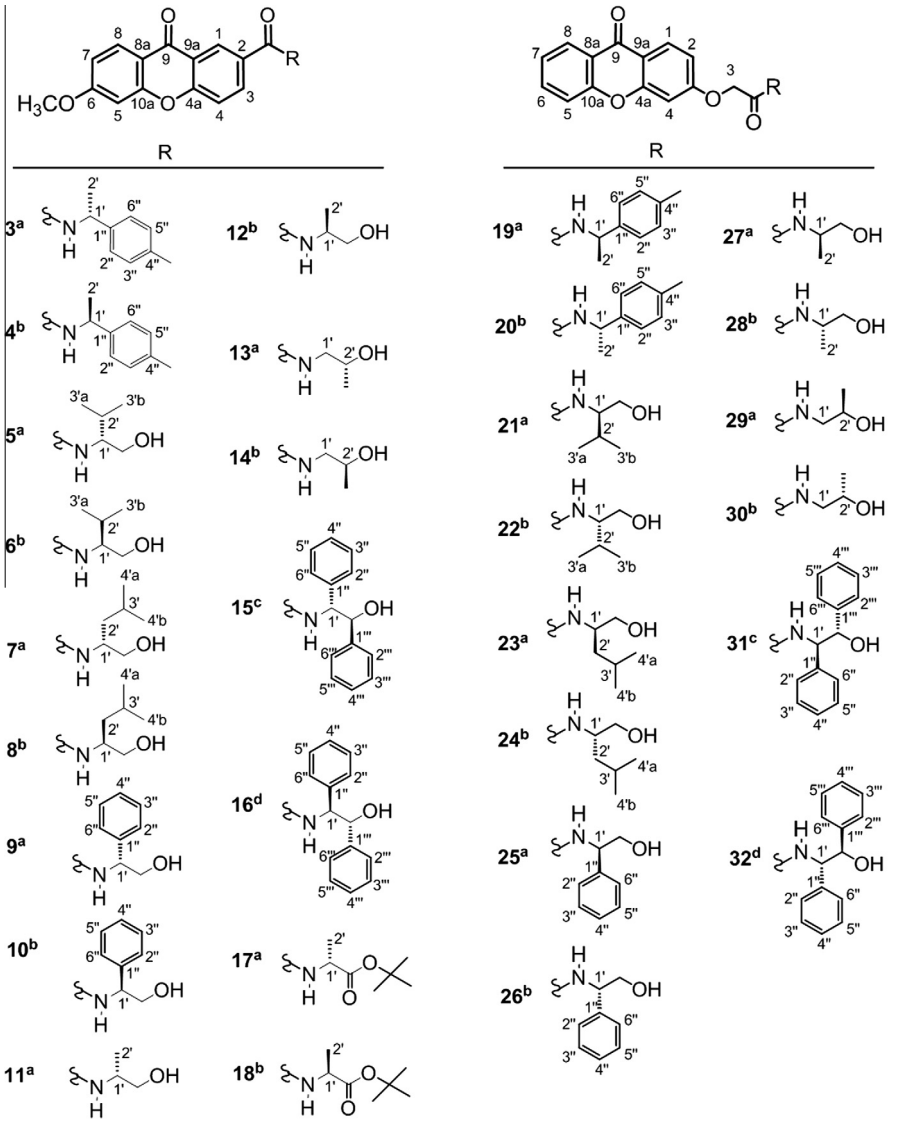
	R	R_1	R_2
1	COOH	H	OCH_3
2	H	OCH_2COOH	H

Figure 1. Structures of carboxyxanthone **1** and carboxymethoxyxanthone **2** used as chemical substrates.

of only one enantiomer is required.[3] However, if both enantiomers are required two independent syntheses are necessary, which is usually a difficult task when specific and expensive reagents, such as asymmetric catalysts, enzymes, chiral auxiliaries, are needed. Besides, the enantiomeric purity of the final product usually is not high. On the other hand, the strategy to obtain pure enantiomers using commercially available chiral reagent in enantiomerically pure form as building blocks can be an interesting approach to obtain both enantiomers in high enantiomeric purity.

Xanthone (9*H*-xanthon-9-one) derivatives comprise an important class of oxygenated heterocycles associated to a large spectrum of biological and pharmacological activities.[4–9] For the last several years, searching of new xanthone derivatives with potential biological/pharmacological properties has remained in the area of interest of our group.[5–18] Despite the massive research regarding xanthone derivatives, there are few examples in the literature concerning synthetic chiral derivatives of xanthones (CDXs).[17,19–24] Among them there are, for example, chiral xanthonolignoids with an inhibitory effect on the *in vitro* growth of different human tumor cell lines.[17] Moreover, the referred biological activity demonstrated to be dependent on the stereochemistry.[25]

In this paper we report the synthesis of CDXs in enantiomerically pure form by coupling two carboxyxanthone derivatives, 6-methoxy-9-oxo-9*H*-xanthene-2-carboxylic acid (**1**) and 2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetic acid (**2**) (Fig. 1), with both enantiomers of eight commercially available chiral building blocks, using *O*-(benzotriazol-1-yl)-*N*-*N*-*N*′-*N*′-tetramethyluronium



[a](*R*)-enantiomer; [b](*S*)-enantiomer; [c](*R*,*S*)-enantiomer; [d](*S*,*R*)-enantiomer

Figure 2. Structures of CDXs **3**–**32** (the used numbering concerns the NMR assignments).

tetrafluoroborate (TBTU) as the coupling reagent. This methodology required mild reaction conditions, was straightforwardly and very high yields were achieved with any degree of racemisation. Thirty CDXs were obtained (Fig. 2) with six (**15**–**18**, **31** and **32**) being here described for the first time. The synthesized CDXs, in enantiomerically pure form, were evaluated for their effect on the *in vitro* growth of three human tumor cell lines namely A375-C5 (melanoma), MCF-7 (breast adenocarcinoma), and NCI-H460 (non-small cell lung cancer). The structural aspects, concerning the nature and positions of substituents on the xanthonic scaffold as well as the stereochemistry of the library of CDXs, are discussed. Some considerations regarding structure–activity relationship are also described.

2. Results and discussion

2.1. Chemistry

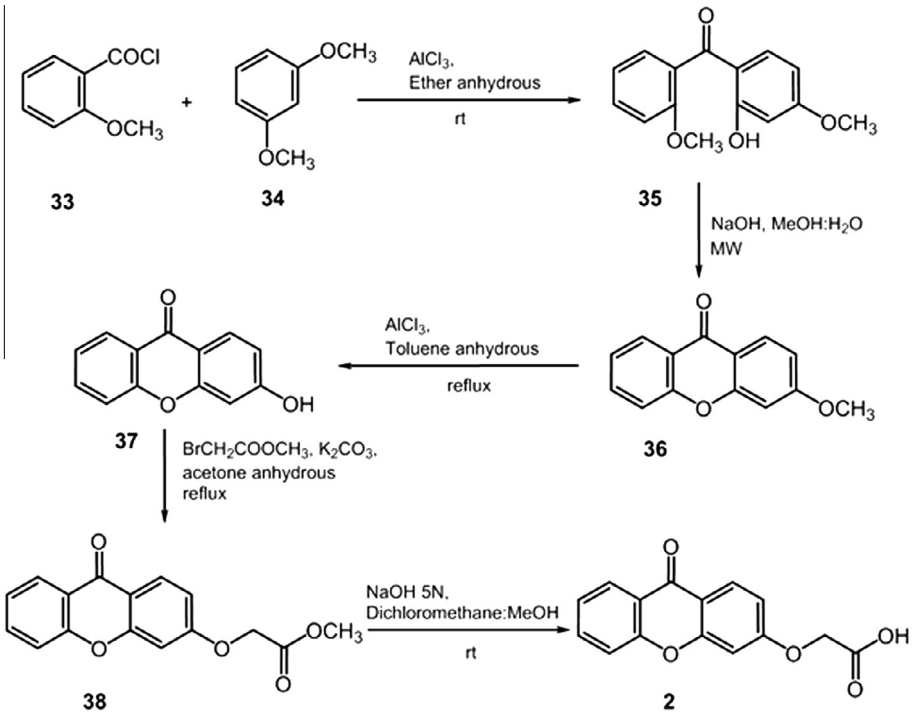
2.1.1. Synthesis of carboxyxanthone derivatives 1 and 2

Carboxyxanthone derivatives are not only interesting bioactive compounds[26,27] but they are also very important as basis to molecular modifications tending to obtain new chiral derivatives.[19] The carboxyxanthone **1** was obtained in our group *via* Ullmann reaction, with the formation of a diaryl ether intermediate, as described elsewhere.[28] The carboxymethoxyxanthone **2** was synthesized *via* a benzophenone intermediate by a multi-step pathway as illustrated on Scheme 1. The syntheses of the benzophenone **35**[29] as well as the 3-methoxy-9*H*-xanthen-9-one (**36**)[29,30] and 3-hydroxy-9*H*-xanthen-9-one (**37**) intermediates have already been described.[30] However, in order to decrease the reaction time and to improve the yield, the alkaline cyclization of the benzophenone **35** was carried out under microwave (MW) irradiation instead of conventional heating. With MW methodology, the reaction time was reduced from 36 h to 30 min. Furthermore, the yield of the synthesis of 3-methoxy-9*H*-xanthen-9-one (**36**) increased from 83% to 92%. The methyl 2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetate (**38**) (described here for the first time) was obtained by Williamson ether synthesis, based on the nucleophilic substitution of 3-hydroxy-9*H*-xanthen-9-one (**37**) with methyl bromoacetate in alkaline medium (Scheme 1). The methyl ester **38** was then hydrolyzed providing the carboxymethoxyxanthone building block **2**. To our best knowledge, the synthesis of the carboxymethoxyxanthone **2** through the alkaline cyclization of the benzophenone intermediate (**35**) using MW irradiation is described here for the first time.

2.1.2. Synthesis of chiral derivatives of xanthones 3–32

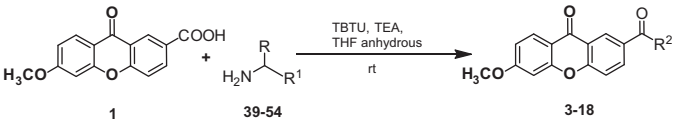
In the course of our studies aiming to enlarge our library of new biologically active CDXs, we were interested in establishing an efficient, practical, and mild methodology for coupling carboxyxanthone derivatives with enantiomerically pure chiral building blocks through an amide bond. Amines, amino alcohols and amino esters as building blocks were chosen to demonstrate the efficiency and applicability of our methodology.

Activation of a carboxyl group for the formation of amide bonds can be achieved either by conversion into more reactive functional groups such as acyl halide, anhydride, acyl azide or by *in situ* activation using coupling reagents. In the case of the carboxylic acid groups on the xanthones **1**–**2**, using tionyl chloride to obtain the respective acyl halides, an extensive degradation of the chemical substrates was observed. In the past few years, the design and synthesis of innovative coupling reagents has been an area of intense investigation and several became commercially available.[31–34] Among of them, the coupling reagent dicyclo-hexylcarboiimide (DCC) was used in the scope of this study and furnished the desirable products; however, the formation of the secondary product dicyclohexylurea led to very low yields (data not shown). Nowadays, the most popular coupling reagents are probably onium (phosphonium and uronium) salts.[35] One of them, TBTU demonstrated to be very efficient for the synthesis of different classes of compounds such as peptides,[36] amides,[37,38] phenylhydrazides,[37] esters,[39,40] 1,3,4, oxadiazoles,[41] acid azides,[42] and thiol esters.[43] This coupling reagent was also employed by our group to successfully synthesize of thirty CDXs (**3**–**32**) by coupling reactions of two different carboxyxanthone derivatives (**1** and **2**) with a variety of

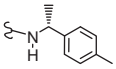
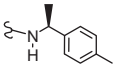
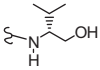
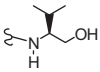
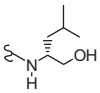
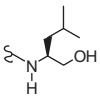
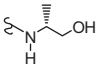
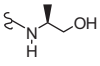
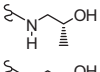
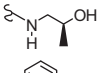
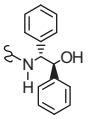
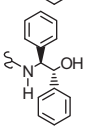
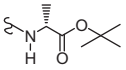
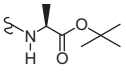


Scheme 1. Total synthesis of carboxymethoxyxanthone **2**.

Table 1
Synthesis of CDXs **3**–**18** by coupling reactions of carboxyxanthone **1** with chiral compounds **39**–**54**



1 39-54 3-18

Compound	R	R^1	Compound	R^2	Time (h)	Yield (%)	ee (%)
39[a]	CH_3		**3**[a]		0.5	98	>99
40[b]	CH_3		**4**[b]		0.5	97	>98
41[a]	$CH(CH_3)_2$	CH_2OH	**5**[a]		2	96	>99
42[b]	$CH(CH_3)_2$	CH_2OH	**6**[b]		2	98	>99
43[a]	$CH_2CH(CH_3)_2$	CH_2OH	**7**[a]		2	98	>99
44[b]	$CH_2CH(CH_3)_2$	CH_2OH	**8**[b]		2	99	>99
45[a]		CH_2OH	**9**[a]		3	96	>99
46[b]		CH_2OH	**10**[b]		3	95	>99
47[a]	CH_3	CH_2OH	**11**[a]		0.5	97	>99
48[b]	CH_3	CH_2OH	**12**[b]		0.5	96	>99
49[a]	H	$CH(CH_3)OH$	**13**[a]		0.5	96	>99
50[b]	H	$CH(CH_3)OH$	**14**[b]		0.5	97	>99
51[c]			**15**[c]		5	94	>97
52[d]			**16**[d]		5	95	>98
53[a]	CH_3	$COOC(CH_3)_3$	**17**[a]		4	96	>99
54[b]	CH_3	$COOC(CH_3)_3$	**18**[b]		4	97	>99

[a] (*R*)-Enantiomer.
[b] (*S*)-Enantiomer.
[c] (*R*,*S*)-Enantiomer.
[d] (*S*,*R*)-Enantiomer.

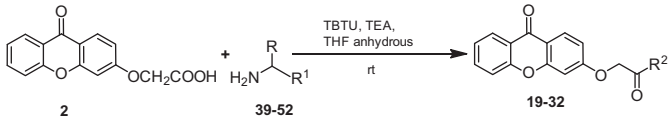
commercially available chiral blocks, namely (*R*)-(+)-α-dimethylbenzylamine (**39**), (*S*)-(−)-α-dimethylbenzylamine (**40**), (*R*)-(−)-valinol (**41**), (*S*)-(+)-valinol (**42**), (*R*)-(−)-leucinol (**43**), (*S*)-(+)-leucinol (**44**), (*R*)-(−)-α-phenylglycinol (**45**), (*S*)-(+)-α-phenylglycinol (**46**), (*R*)-(−)-2-amino-1-propanol (**47**), (*S*)-(+)-2-amino-1-propanol (**48**), (*R*)-(−)-1-amino-2-propanol (**49**), (*S*)-(+)-1-amino-2-propanol (**50**), (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol (**51**), (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol (**52**), (*R*)-alanine *tert*-butyl ester (**53**),

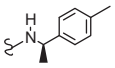
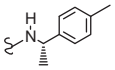
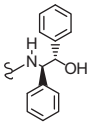
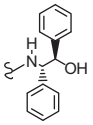
(*S*)-alanine *tert*-butyl ester (**54**) (Tables 1 and 2). Our selection included both enantiomers of enantiomerically pure building blocks with no tendency towards racemization or enantiomeric interconversion, and having a primary amine as reactive group for amide formation. The coupling reactions were performed in anhydrous THF using equivalent amounts of the carboxyxanthone derivative substrate, the corresponding commercial chiral block and TBTU at room temperature with 2 equiv of TEA.

As shown in Tables 1 and 2, the syntheses worked equally well with both carboxyxanthone derivatives (**1** and **2**) affording the desired amides in excellent yields (ranging from 94% to 99%). Actually, TBTU can also be used at room temperature for the synthesis of esters from carboxylic acids and either aliphatic alcohols or phenols in the presence of organic bases.[39,40] Interestingly, according to these yields, the coupling reactions with chiral amino alcohols (**41**–**52**) were highly selective for the more nucleophilic group of the building blocks, that is, the amine instead of the alcohol group.

Regarding the reaction times, some differences were observed. Indeed, the coupling reactions with the amines or amino alcohols

Table 2
Synthesis of CDXs **19**–**32** by coupling reactions of carboxymethoxyxanthone **2** with chiral compounds **39**–**52**



Compound	R	R^1	Compound	R^2	Time (h)	Yield (%)	ee (%)
39[a]	CH_3		**19**[a]		0.5	97	>99
40[b]	CH_3		**20**[b]		0.5	96	>98
41[a]	$CH(CH_3)_2$	CH_2OH	**21**[a]		2	95	>99
42[b]	$CH(CH_3)_2$	CH_2OH	**22**[b]		2	97	>99
43[a]	$CH_2CH(CH_3)_2$	CH_2OH	**23**[a]		2	98	>99
44[b]	$CH_2CH(CH_3)_2$	CH_2OH	**24**[b]		2	96	>99
45[a]		CH_2OH	**25**[a]		3	94	>99
46[b]		CH_2OH	**26**[b]		3	95	>99
47[a]	CH_3	CH_2OH	**27**[a]		0.5	97	>99
48[b]	CH_3	CH_2OH	**28**[b]		0.5	96	>99
49[a]	H	$CH(CH_3)OH$	**29**[a]		0.5	98	>99
50[b]	H	$CH(CH_3)OH$	**30**[b]		0.5	97	>99
51[c]			**31**[c]		5	95	>98
52[d]			**32**[d]		5	94	>99

[a] (*R*)-Enantiomer.
[b] (*S*)-Enantiomer.
[c] (*R*,*S*)-Enantiomer.
[d] (S,*R*)-Enantiomer.

bearing alkyl groups were faster and completed after 0.5–2 h, while the reactions involving amino esters or amino alcohols bearing aryl groups were only completed after 3–5 h. However, concerning the amino alcohols bearing alkyl groups, it was found that increasing the size of the alkyl group, reaction times also augmented. For example, the coupling reactions for amino alcohols with a methyl group (**47**–**50**) were completed after 0.5 h, while the reactions for amino alcohols with an isopropyl group (**41**–**42**) needed 2 h to be completed. Furthermore, the coupling reactions with the amino alcohols possessing two aryl groups in the chiral moiety (**51**–**52**) were slower (5 h) compared with the reactions involving amino alcohols with one aryl group (3 h) (**45**–**46**). It can be inferred, that the steric hindrance created by the bulky alkyl groups and aryl groups of the amino alcohols may be responsible for the observed results.

The purification procedures were easy, involving simple washing of the crude reaction products with 1 M HCl solution and saturated solution of $NaHCO_3$ to remove the by-product 1-hydroxybenzotriazole, as well as the excess of reagents, followed by recrystallization from ethyl acetate/*n*-hexane or EtOH or chloroform/*n*-hexane to afford the CDXs.

HPLC using different types of CSPs was used to determine the enantiomeric purity of the synthesized CDXs (Tables 1 and 2; see Section 4 for details). The HPLC methods development are described elsewhere.[44,45]

Thus, the synthetic methodology used herein provides to be very efficient, broad-scope applicability, inexpensive and operationally simplest for obtaining both enantiomers with high ee. Additionally, the synthesis procedure can be easily scaled-up for both enantiomers in order to obtain available quantities for biological/pharmacological assays.

2.2. Biological evaluation

2.2.1. Effect on the growth of human tumor cell lines

The library of thirty CDXs, in enantiomerically pure form, were evaluated on the *in vitro* growth of three human tumor cell lines: A375-C5 (melanoma), MCF-7 (breast adenocarcinoma), and NCI-H460 (non-small cell lung cancer). This drug-screening procedure, adopted from the National Cancer Institute (NCI, USA), uses the protein binding dye, SRB, to assess cell growth.[46] For each compound, a dose–response curve was established. The results, expressed as the concentration that was able to cause 50% cell growth inhibition (GI_{50}), are summarized in Table 3.

The overall results obtained demonstrate that some CDXs exhibited interesting growth inhibitory effects on the tested human tumor cell lines. Actually, the most active CDX in all human tumor cell lines was compound **15** presenting values of GI_{50} = 32.15 ± 2.03 μM, GI_{50} = 22.55 ± 1.99 μM and GI_{50} = 14.05 ± 1.82 μM for A375-C5, MCF-7, and NCI-H460, respectively.

Moreover, the evaluation of the growth inhibitory effect of the series of CDXs synthesized by coupling the carboxyxanthone **1** with different chiral amino alcohols (CDXs **5**–**16**) allowed taking some considerations regarding structure–activity relationship. Accordingly, it was found that the CDXs bearing aryl groups in the chiral moiety (**9**–**10**, **15**–**16**) were the most active compounds in all human tumor cell lines tested. However, a slight decrease of activity was observed for the CDXs possessing only one aryl group (**9** and **10**) when compared with the CDXs possessing two aryl groups (**15** and **16**). Regarding the CDXs bearing alkyl groups in the chiral moiety (**5**–**8**, **11**–**14**) it was observed that decreasing the size of the alkyl group the growth inhibitor effect also decreased or was abolished. For example, the CDXs with an isopropyl group in the chiral moiety, namely CDXs **7** and **8** presented values

Table 3
Growth inhibitory activity of thirty CDXs on the growth of three human tumor cell lines

Compound	GI_{50} (μM)		
	A375-C5 (melanoma)	MCF-7 (breast adenocarcinoma)	NCI-H460 (non-small cell lung cancer)
3	>150	>150	85.88 ± 5.30
4	>150	91.91 ± 6.27	42.62 ± 1.77
5	102.10 ± 1.24	125.34 ± 9.81	114.06 ± 3.80
6	>150	>150	>150
7	112.94 ± 8.38	112.96 ± 7.10	100.96 ± 11.35
8	69.72 ± 0.03	63.33 ± 3.51	62.61 ± 3.86
9	57.72 ± 2.90	54.25 ± 3.06	53.88 ± 3.89
10	45.95 ± 5.84	43.22 ± 6.51	43.32 ± 4.97
11	>150	>150	>150
12	>150	>150	>150
13	>150	>150	>150
14	>150	127.63 ± 19.93	>150
15	32.15 ± 2.03	22.55 ± 1.99	14.05 ± 1.82
16	51.69 ± 5.77	36.54 ± 2.95	24.88 ± 1.37
17	>150	>150	>150
18	>150	>150	>150
19	>150	>150	>150
20	>150	>150	>150
21	134.17 ± 9.77	>150	>150
22	114.55 ± 16.65	>150	>150
23	105.05 ± 13.45	94.88 ± 9.17	92.17 ± 9.42
24	79.37 ± 4.26	65.78 ± 7.76	63.73 ± 6.77
25	66.24 ± 2.59	71.37 ± 3.95	67.75 ± 2.38
26	46.27 ± 6.14	46.69 ± 2.03	38.75 ± 4.92
27	134.74 ± 7.79	>150	>150
28	>150	>150	133.63 ± 9.81
29	>150	>150	>150
30	>150	>150	>150
31	>150	>150	>150
32	>150	>150	>150

*Results are presented as GI_{50} after a continuous exposure of 48 h and represent means ± SEM from at least three independent experiments performed in duplicate. Doxorubicin was used as positive control, GI_{50}: A375-C5 = 136.20 ± 12.13 nM; MCF-7 = 59.77 ± 3.81 nM; NCI-H460 = 34.07 ± 1.95 nM.

of GI_{50} = 112.94 ± 8.38 μM and GI_{50} = 62.72 ± 0.03 μM for A375-C5, while the CDXs with a methyl group (**11**–**14**) were inactive (GI_{50} >150 μM). Thus, it can be inferred that the presence of aryl or bulky alkyl groups in the chiral moiety may be important for the activity.

Furthermore, comparing the results obtained with the CDXs **15**–**16** and the CDXs **31**–**32**, possessing the same chiral moiety while the xanthonic chemical substrates is the carboxyxanthone **1** and carboxymethoxyxanthone **2**, respectively, it can be seen that: the first pair of compounds exhibited the highest growth inhibitory effects on the three human tumor cell lines, while the second pair was inactive. Accordingly, it is interesting to point out that the nature of the substituents and their positions on the xanthonic scaffold also have an important role in growth inhibitory effect.

Regarding the influence of the enantiomeric configuration on the activity, enantioselectivity between the enantiomeric pairs of CDXs **7**–**8** and **15**–**16**, on the three human tumor cell lines, were observed. For example, the CDX **7** presented a significant ($p < 0.01$) weaker activity for all cell lines tested (GI_{50} = 112.94 ± 8.38 μM, GI_{50} = 112.96 ± 7.10 μM and GI_{50} = 100.96 ± 11.35 μM for A375-C5, MCF-7 and NCI-H460 respectively), while its enantiomer (CDX **8**) was more active presenting values of GI_{50} = 69.72 ± 0.03 μM, GI_{50} = 63.33 ± 3.51 μM and GI_{50} = 62.61 ± 3.86 μM for A375-C5, MCF-7 and NCI-H460, respectively.

Another interesting example of enantioselectivity was observed between the enantiomers **3** and **4** in MCF-7 and NCI-H460 human tumor cell lines. In fact, considering NCI-H460 cell line, CDX **3** presented a slight inhibitory activity (GI_{50} = 85.88 ± 5.30 μM), while CDX **4** was able to inhibit the growth of this cell line with a GI_{50} = 42.62 ± 1.77 μM; in MCF-7 cell line, CDX **3** was considered not active (GI_{50} >150 μM), while CDX **4** presented a weaker activity (GI_{50} = 91.91 ± 6.27 μM) ($p < 0.01$). Considering these results as well as the incapacity of both enantiomers to inhibit the growth of the human tumor cell line A375-C5, it can be emphasized that cell-type selectivity also occurred.

3. Conclusions

Coupling reactions of carboxyxanthone derivatives with a variety of chiral building blocks, such as amines, amino alcohols, and amino esters demonstrated to be very efficient under very mild conditions using TBTU. Six new and twenty four previously described chiral derivatives of xanthones were synthesized with excellent yields, very high enantiomeric excess and requiring short reaction times. The present methodology has also the advantages of operational simplicity, use of ready available, inexpensive and low toxic materials, and simple reaction work-up. The MW-assisted organic synthesis was successfully applied in the alkaline cyclization of a benzophenone intermediate, with an increased yield and a remarkable shorter reaction time, when compared with the conventional heating conditions.

Some CDXs exhibited interesting dose-dependent growth inhibitory effects on the evaluated human tumor cell lines. Furthermore, it can be inferred that the effects on the growth of the human tumor cell lines can be ascribed not only to the nature and positions of substituents on the xanthonic scaffold, but also are associated with the stereochemistry of the CDXs concerning enantioselectivity in some cases.

4. Experimental

4.1. General

Melting points are uncorrected and were obtained in a Köfler microscope. IR spectra were recorded on an ATIMattson Genesis series FTIR (software: WinFirst v.2.10) spectrophotometer in KBr microplates (cm^{-1}). ^1H and ^{13}C NMR spectra were taken in $CDCl_3$ or DMSO-d_6 at room temperature on Bruker Avance 300 instrument (300.13 or 500.13 MHz for ^1H and 75.47 or 125.77 MHz for ^{13}C). Chemical shifts are expressed in δ (ppm) values relative to tetramethylsilane (TMS) as an internal reference. Coupling constants are reported in hertz (Hz). ^{13}C NMR assignments were made by 2D HSQC and HMBC experiments (long-range C, H coupling constants were optimized to 7 and 1 Hz). MS spectra were recorded as EI (electronic impact) mode on a VG Autospec Q spectrometer (m/z) and HRMS mass spectra were measured on a Bruker Daltonics micrOTOF Mass Spectrometer, recorded as ESI (electrospray) mode in Centro de Apoio Científico e Tecnolóxico á Investigation (C.A.C.T.I.), University of Vigo, Spain. TLC was performed using Merck silica gel 60 (GF_{254}) plates, with appropriate mobile phases and detection at 254 and/or 365 nm. Column chromatography was carried out using Merck silica gel 60 (0.040–0.063 mm). Optical rotation measurements were carried out on a Polartronic Universal polarimeter. Liquid chromatography was performed using a HPLC system consisted of two Shimadzu LC 10-ADvp pumps, a FCV-10AL solvent selector valve, an automatic injector SIL10-Advp, a SPD-10AV UV/VIS detector with a SCL-10Avp interface or a HPLC system consisted of two Shimadzu LC 10-AD pumps, an automatic injector SIL10-AF, a SPD-10A UV/VIS detector with a CBM-10A interface or a System 880-PU Intelligent HPLC Pump (Jasco) equipped with a Rheodyne 7125 injector fitted with a 20 μL loop, a 875-UV Intelligent UV/VIS Detector, and a Chromatography Station for Windows, version 1.7 DLL. Chirobiotic T column (15 × 0.46 cm ID size column) was commercially available from Sigma-Aldrich. Polysaccharide columns were prepared as described elsewhere[47,48] and consisted of amylose tris-3,5-dimethylphenylcarbamate and cellulose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), and packed into a stainless-steel 15 × 0.46 cm ID size column. (*S*,*S*)-Whelk-O1 column (15 × 0.46 cm ID size column) was commercially available from Regis Technologies, Inc. Both enantiomers of the optically pure reagents, valinol, leucinol, 2-amino-1-propanol, 1-amino-2-propanol, α-phenylglycinol, 2-amino-1,2-diphenylethanol, alanine *tert*-butyl ester and α-dimethylbenzylamine, were obtained from Fluka or Sigma–Aldrich. Other reagents and solvents were commercially available materials at *pro analysis* or HPLC grade, from Sigma–Aldrich, Merck or Fluka, and used without further purification. MW reactions were performed using an Ethos MicroSYNTH 1600 Microwave Labstation from Milestone (ThermoUnicam, Portugal).

4.2. Synthesis of the carboxyxanthone 6-methoxy-9-oxo-9*H*-xanthene-2-carboxylic acid (1)

Compound **1** was obtained *via* Ullmann reaction as described elsewhere.[28]

4.3. Synthesis of the carboxymethoxyxanthone 2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetic acid (2) and intermediates 35–38

The synthetic route used to synthesize compound **2** is outlined in Scheme 1, which involved a multi-step pathway.

4.3.1. (2-Hydroxy-4-methoxyphenyl)(2-methoxyphenyl)methanone (35)

Compound **35** was synthesized (9.42 g, 62%) and characterized according to the described procedure.[29]

4.3.2. 3-Methoxy-9*H*-xanthen-9-one (36)

A mixture of compound **35** (10.00 g, 38.76 mmol) and NaOH (18.80 g, 0.47 mol) was placed into a 270 mL Teflon reactor,

provided with a fiber-optic probe sensor, and MeOH/water (150 mL, 2:1 v:v) were added. The mixture was submitted to 30 min of microwave (MW) irradiation at 300 W of potency. After cooling, the solid was filtered and washed with water (100 mL). The crude product was recrystallized from MeOH to afford the compound **36** as a white solid (5.69 g, 65%). Compound **36** was characterized according to the described procedure.[30]

4.3.3. 3-Hydroxy-9*H*-xanthen-9-one (37)

Compound **37** was synthesized (7.13 g, 76%)[49] and characterized[30] according to the described procedure.

4.3.4. Methyl 2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetate (38)

Compound **37** (10.00 g, 47.17 mmol) was dissolved in anhydrous acetone (400 mL) and K_2CO_3 (7.65 g, 55.43 mmol) and $BrCH_2COOCH_3$ (5 mL, 54.38 mmol) were added. The mixture was kept under reflux and magnetic stirring for 24 h. Then, the mixture was concentrated under reduced pressure and *n*-hexane was added. The solid was separated by filtration and purified by column chromatography (silica gel, dichloromethane/ethyl acetate in gradient) to afford compound **38** as a white solid (9.11 g, 68%); mp: 156–159 °C; IR (KBr): $\tilde{\nu}$ 1737, 1617, 1463, 1433, 1378, 1291, 1244, 821, 760 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.19 (1H, dd, J = 7.4 and 0.9 Hz, H-8), 8.13 (1H, d, J = 9.0 Hz, H-1), 7.87 (1H, ddd, J = 8.0, 7.8 and 1.2 Hz, H-6), 7.65 (1H, d, J = 8.1 Hz, H-5), 7.50 (1H, ddd, J = 7.5, 7.3 and 0.9 Hz, H-7), 7.21 (1H, d, J = 2.4 Hz, H-4), 7.12 (1H, dd, J = 8.8 and 2.4 Hz, H-2), 5.06 (2H, s, OCH_2), 3.75 ppm (3H, s, OCH_3); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 168.6 (C=O, ester), 163.2 (C-3), 157.3 (C-4a), 155.6 (C-10a), 135.2 (C-6), 127.7 (C-1), 125.9 (C-8), 124.4 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.5 (C-9a), 113.8 (C-2), 101.6 (C-4), 65.0 (OCH_2), 52.0 ppm (OCH_3); MS (ESI) m/z (%): 286 $[M+H]^+$+1 (20), 285 $[M+H]^+$ (100), 201 (15), 175 (12), 158 (73), 130 (18); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{12}O_5$: 285.07575, found: 285.07629.

4.3.5. 2-((9-Oxo-9*H*-xanthen-3-yl)oxy)acetic acid (2)

Compound **38** (9.40 g, 33.07 mmol) was dissolved in dichloromethane/MeOH (800 mL, 1:1 v/v) and 5 M NaOH solution (64 mL) was added. The mixture was kept at room temperature and magnetic stirring for 5 h. After this period, the dichloromethane and MeOH were evaporated under reduced pressure and the suspension was washed with dichloromethane (2 × 100 mL). The aqueous phase was acidified with 5 M HCl solution resulting in the formation of a precipitate that was collected by filtration under reduced pressure and dissolved in saturated $NaHCO_3$ solution. This solution was washed again with dichloromethane (2 × 100 mL) and the aqueous phase was acidified with 5 M HCl solution. The precipitate formed was collected by filtration under reduced pressure, washed with water, and recrystallized from MeOH to provide compound **2** as a white solid (6.96 g, 78%); mp: 211–213 °C (MeOH); IR (KBr): $\tilde{\nu}$ 2858, 1712, 1609, 1461, 1431, 1374, 1231, 852, 751 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 13.32 (1H, s, COO*H*), 8.19 (1H, dd, J = 7.4 and 0.9 Hz, H-8), 8.13 (1H, d, J = 9.0 Hz, H-1), 7.87 (1H, ddd, J = 8.2, 7.8 and 1.2 Hz, H-6), 7.65 (1H, d, J = 8.4 Hz, H-5), 7.49 (1H, ddd, J = 7.5, 7.3 and 0.9 Hz, H-7), 7.16 (1H, d, J = 2.4 Hz, H-4), 7.11 (1H, dd, J = 8.8 and 2.4 Hz, H-2), 4.94 ppm (2H, s, OCH_2); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 169.5 (*C*OOH), 163.4 (C-3), 157.3 (C-4a), 155.6 (C-10a), 135.2 (C-6), 127.7 (C-1), 125.9 (C-8), 124.4 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.3 (C-9a), 113.8 (C-2), 101.5 (C-4), 65.0 ppm (OCH_2); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{10}O_5$: 271.06010, found: 271.06006.

4.4. General procedure for the synthesis of chiral derivatives of xanthones 3–32

6-Methoxy-9-oxo-9*H*-xanthene-2-carboxylic acid (**1**) or 2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetic acid (**2**) (100 mg, 0.37 mmol) was dissolved in anhydrous THF (20 mL) and TEA (103 μL, 0.74 mmol) was added. Following, TBTU (120 mg, 0.37 mmol) and an appropriate chiral reagent (0.37 mmol) were added. The mixture was stirred at room temperature for 0.5 to 5 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude product was dissolved in 50 mL of dichloromethane (**3**–**10**, **13**–**14**, **17**–**30**), ethyl acetate (**11**–**12**) or chloroform (**15**–**16**, **31**–**32**). This solution was washed with 1 M HCl solution (2 × 25 mL), saturated solution of $NaHCO_3$ (2 × 30 mL), and water (3 × 50 mL). The organic layer was dried with anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The product was recrystallized from ethyl acetate/*n*-hexane (**3**–**4**, **7**–**14**, **19**–**20**, **23**–**30**), EtOH (**5**–**6**, **21**–**22**), chloroform/*n*-hexane (**15**–**16**, **31**–**32**), or MeOH/water (**17**–**18**) to afford the chiral derivative of xanthone. Compounds **3**–**32** were identified by their spectroscopic and analytical data.

4.4.1. (*R*)-6-Methoxy-9-oxo-*N*-(1-(*p*-tolyl)ethyl)-9*H*-xanthene-2-carboxamide (3)

Compound **3** was obtained as a white solid (140 mg, 98%); mp: 221–223 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −125.3 (c = 10.70 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3336, 1660, 1611, 1531, 1477, 1440, 1269, 836 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.56 (1H, d, J = 2.3 Hz, H-1), 8.32 (1H, dd, J = 8.7 and 2.3 Hz, H-3), 8.25 (1H, d, J = 8.9 Hz, H-8), 7.53 (1H, d, J = 8.7 Hz, H-4), 7.31 (2H, d, J = 8.0 Hz, H-2″ and H-6″), 7.18 (2H, d, J = 8.0 Hz, H-3″ and H-5″), 6.99 (1H, dd, J = 8.9 and 2.3 Hz, H-7), 6.92 (1H, d, J = 2.3 Hz, H-5), 6.59 (1H, d, J = 7.4 Hz, N*H*), 5.32 (1H, m, H-1′), 3.95 (3H, s, Ar-OCH_3), 2.34 (3H, s, Ar-CH_3), 1.63 ppm (3H, d, J = 6.9 Hz, H-2′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 175.9 (C-9), 165.5 (*C*=O, amide), 164.8 (C-6), 158.0 (C-10a), 157.9 (C-4a), 139.9 (C-1″), 137.2 (C-4″), 134.3 (C-3), 130.1 (C-2), 129.4 (C-3″ and C-5″), 128.3 (C-8), 126.2 (C-2″ and C-6″), 124.0 (C-1), 121.0 (C-9a), 118.5 (C-4), 115.5 (C-8a), 113.8 (C-7), 100.3 (C-5), 55.9 (Ar-O*C*H$_3$), 49.3 (C-1′), 21.7 (Ar-*C*H$_3$), 21.1 ppm (C-2′); MS (ESI) m/z (%): 389 $[M+H]^+$+1 (29), 388 $[M+H]^+$ (100), 354 (23), 326 (38), 270 (9), 219 (17), 197 (6); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{21}NO_4$: 388.15433, found: 388.15343; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: EtOH/ACN (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

4.4.2. (*S*)-6-Methoxy-9-oxo-*N*-(1-(*p*-tolyl)ethyl)-9*H*-xanthene-2-carboxamide (4)

Compound **4** was synthesized (139 mg, 97%) and characterized according to the described procedure.[28]

4.4.3. (*R*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (5)

Compound **5** was obtained as a white solid (126 mg, 96%); mp: 180–182 °C (EtOH); $[\alpha]_D^{25°C}$ +14.8 (c = 10.08 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3370, 3241, 1655, 1619, 1539, 1474, 1444, 1270, 828 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.73 (1H, d, J = 2.3 Hz, H-1), 8.38 (1H, d, J = 8.7 Hz, N*H*), 8.31 (1H, dd, J = 8.7 and 2.3 Hz, H-3), 8.15 (1H, d, J = 8.9 Hz, H-8), 7.71 (1H, d, J = 8.7 Hz, H-4), 7.21 (1H, d, J = 2.3 Hz, H-5), 7.10 (1H, dd, J = 8.9 and 2.3 Hz, H-7), 4.65 (1H, t, J = 5.6 Hz, O*H*), 3.95 (3H, s, Ar-OCH_3), 3.85 (1H, m, H-1′), 3.56 (2H, m, CH_2OH), 1.97 (1H, m, H-2′), 0.93 (3H, d, J = 7.0 Hz, H-3′a)*, 0.91 ppm (3H, d, J = 7.0 Hz,

H-3′b)*; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 165.2 (*C*=O, amide), 165.1 (C-6), 157.6 (C-10a), 157.1 (C-4a), 134.1 (C-3), 130.9 (C-2), 127.8 (C-8), 125.4 (C-1), 120.7 (C-9a), 118.0 (C-4), 115.0 (C-8a), 114.0 (C-7), 100.8 (C-5), 61.3 (*C*H$_2$OH), 57.0 (Ar-O*C*H$_3$), 56.3 (C-1′), 28.7 (C-2′), 19.7 (C-3′a)*, 18.8 ppm (C-3′b)*; MS (ESI) *m*/*z* (%): 357 [*M*+H]$^+$+1 (28), 356 [*M*+H]$^+$ (100), 326 (27), 255 (70), 233 (36), 197 (3), 155 (10); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{20}H_{21}NO_5$: 356.14925, found: 356.14967; ee >99% (HPLC; Column: Chirobiotic T, Mobile phase: *n*-hexane/EtOH (80:20 v:v), 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.4. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (6)

Compound **6** was synthesized (129 mg, 98%) and characterized according to the described procedure.[28]

4.4.5. (*R*)-*N*-(1-Hydroxy-4-methylpentan-2-yl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (7)

Compound **7** was obtained as a white solid (134 mg, 98%); mp: 156–158 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +25.0 (c = 11.40 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3360, 3283, 1651, 1617, 1546, 1468, 1443, 1261, 801 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 8.71 (1H, d, J = 2.1 Hz, H-1), 8.40 (1H, d, J = 8.6 Hz, N*H*), 8.30 (1H, dd, J = 8.7 and 2.2 Hz, H-3), 8.14 (1H, d, J = 8.9 Hz, H-8), 7.70 (1H, d, J = 8.7 Hz, H-4), 7.21 (1H, d, J = 2.2 Hz, H-5), 7.10 (1H, dd, J = 8.9 and 2.2 Hz, H-7), 4.76 (1H, t, J = 5.7 Hz, O*H*), 4.12 (1H, m, H-1′), 3.95 (3H, s, Ar-OC*H*$_3$), 3.43 (2H, m, C*H*$_2$OH), 1.63 (2H, m, H-2′), 1.45 (1H, m, H-3′), 0.91 (3H, d, J = 6.0 Hz, H-4′a)*, 0.90 ppm (3H, d, J = 6.0 Hz, H-4′b)*; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 165.2 (*C*=O, amide), 164.7 (C-6), 157.6 (C-10a), 157.1 (C-4a), 134.0 (C-3), 130.7 (C-2), 127.8 (C-8), 125.3 (C-1), 120.7 (C-9a), 118.1 (C-4), 115.0 (C-8a), 114.0 (C-7), 100.8 (C-5), 63.9 (*C*H$_2$OH), 56.3 (Ar-O*C*H$_3$), 49.8 (C-1′), 39.0 (C-2′), 24.5 (C-3′), 23.5 (C-4′a)*, 21.9 ppm (C-4′b)*; MS (ESI) *m*/*z* (%): 371 [*M*+H]$^+$+1 (28), 370 [*M*+H]$^+$ (100), 328 (8), 306 (8), 219 (4), 197 (4), 171 (18); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{21}H_{23}NO_5$: 370.16490, found: 370.16552; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: EtOH/ACN (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.6. (*S*)-*N*-(1-Hydroxy-4-methylpentan-2-yl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (8)

Compound **8** was synthesized (135 mg, 99%) and characterized according to the described procedure.[28]

4.4.7. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (9)

Compound **9** was obtained as a white solid (137 mg, 95%); mp: 94–96 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +75.6 (c = 2.70 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3395, 3255, 1633, 1618, 1544, 1473, 1430, 1258, 816 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 9.12 (1H, d, J = 8.0 Hz, N*H*), 8.80 (1H, d, J = 2.2 Hz, H-1), 8.32 (1H, dd, J = 8.8 and 2.2 Hz, H-3), 8.15 (1H, d, J = 8.9 Hz, H-8), 7.72 (1H, d, J = 8.8 Hz, H-4), 7.42 (2H, d, J = 7.2 Hz, H-2″ and H-6″), 7.33 (2H, t, J = 7.2 Hz, H-3″ and H-5″), 7.25 (1H, d, J = 7.2 Hz, H-4″), 7.21 (1H, d, J = 2.3 Hz, H-5), 7.09 (1H, dd, J = 8.9 and 2.3 Hz, H-7), 5.11 (1H, m, H-1′), 5.03 (1H, t, J = 5.8 Hz, O*H*), 3.95 (3H, s, Ar-OC*H*$_3$), 3.70 ppm (2H, m, C*H*$_2$OH); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 165.3 (*C*=O, amide), 164.8 (C-6), 157.6 (C-10a), 157.2 (C-4a), 141.3 (C-1″), 134.1 (C-3), 130.4 (C-2), 128.2 (C-3″ and C-5″), 127.8 (C-8), 127.1 (C-2″ and C-6″), 127.0 (C-4″), 125.5 (C-1), 120.7 (C-9a), 118.2 (C-4), 115.0 (C-8a), 114.0 (C-7), 100.8 (C-5), 64.5 (*C*H$_2$OH), 56.3 (C-1′), 56.2 ppm (Ar-O*C*H$_3$); MS (ESI) *m*/*z* (%): 391 [*M*+H]$^+$+1 (28), 390 [*M*+H]$^+$ (100), 354 (3), 255 (12), 197 (5), 179 (8); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{23}H_{19}NO_5$: 390.13360, found: 390.13209; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: EtOH/ACN (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

4.4.8. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (10)

Compound **10** was obtained as a white solid (138 mg, 96%); mp: 94–96 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −76.0 (c = 2.70 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3395, 3284, 1633, 1618, 1537, 1475, 1440, 1266, 830 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 9.11 (1H, d, J = 8.0 Hz, N*H*), 8.81 (1H, d, J = 2.2 Hz, H-1), 8.32 (1H, dd, J = 8.8 and 2.2 Hz, H-3), 8.15 (1H, d, J = 8.9 Hz, H-8), 7.72 (1H, d, J = 8.8 Hz, H-4), 7.42 (2H, d, J = 7.1 Hz, H-2″ and H-6″), 7.33 (2H, t, J = 7.1 Hz, H-3″ and H-5″), 7.25 (1H, d, J = 7.1 Hz, H-4″), 7.21 (1H, d, J = 2.3 Hz, H-5), 7.10 (1H, dd, J = 8.9 and 2.3 Hz, H-7), 5.11 (1H, m, H-1′), 5.01 (1H, t, J = 5.8 Hz, O*H*), 3.95 (3H, s, Ar-OC*H*$_3$), 3.70 ppm (2H, m, C*H*$_2$OH); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 165.2 (*C*=O, amide), 164.8 (C-6), 157.5 (C-10a), 157.2 (C-4a), 141.3 (C-1″), 134.1 (C-3), 130.4 (C-2), 128.1 (C-3″ and C-5″), 127.7 (C-8), 127.0 (C-2″ and C-6″), 127.0 (C-4″), 125.4 (C-1), 120.7 (C-9a), 118.1 (C-4), 115.0 (C-8a), 114.0 (C-7), 100.8 (C-5), 64.4 (*C*H$_2$OH), 56.3 (C-1′), 56.2 ppm (Ar-O*C*H$_3$); MS (ESI) *m*/*z* (%): 391 [*M*+H]$^+$+1 (26), 390 [*M*+H]$^+$ (100), 348 (18), 255 (57), 197 (14), 191 (49), 179 (22); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{23}H_{19}NO_5$: 390.13360, found: 390.13331; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: EtOH/ACN (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

4.4.9. (*R*)-*N*-(1-Hydroxypropan-2-yl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (11)

Compound **11** was obtained as a white solid (117 mg, 97%); mp: 233–235 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −83.3 (c = 0.72 × 10^{-6} g/mL in acetone); IR (KBr): $\tilde{\nu}$ 3380, 3312, 1657, 1617, 1551, 1479, 1442, 1265, 821 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 8.71 (1H, d, J = 2.1 Hz, H-1), 8.49 (1H, d, J = 8.1 Hz, N*H*), 8.30 (1H, dd, J = 8.8 and 2.1 Hz, H-3), 8.14 (1H, d, J = 8.9 Hz, H-8), 7.71 (1H, d, J = 8.8 Hz, H-4), 7.21 (1H, d, J = 2.2 Hz, H-5), 7.10 (1H, dd, J = 8.9 and 2.2 Hz, H-7), 4.79 (1H, t, J = 5.7 Hz, O*H*), 4.03 (2H, m, C*H*$_2$OH), 3.95 (3H, s, Ar-OC*H*$_3$), 3.49 (1H, m, H-1′), 1.16 ppm (3H, d, J = 6.7 Hz, H-2′); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 165.2 (*C*=O, amide), 164.4 (C-6), 157.5 (C-10a), 157.1 (C-4a), 134.0 (C-3), 130.6 (C-2), 127.7 (C-8), 125.3 (C-1), 120.6 (C-9a), 118.0 (C-4), 114.9 (C-8a), 114.0 (C-7), 100.8 (C-5), 64.3 (C-1′), 56.3 (Ar-O*C*H$_3$), 47.5 (*C*H$_2$OH), 17.0 ppm (C-2′); MS (ESI) *m*/*z* (%): 329 [*M*+H]$^+$+1 (18), 328 [*M*+H]$^+$ (100), 282 (17), 218 (13); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11798; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: EtOH/ACN (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

4.4.10. (*S*)-*N*-(1-Hydroxypropan-2-yl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (12)

Compound **12** was obtained as a white solid (116 mg, 96%); mp: 233–235 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +83.3 (c = 0.72 × 10^{-6} g/mL in acetone); IR (KBr): $\tilde{\nu}$ 3387, 3312, 1652, 1620, 1543, 1486, 1443, 1261, 819 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 8.72 (1H, d, J = 2.2 Hz, H-1), 8.49 (1H, d, J = 8.0 Hz, N*H*), 8.30 (1H, dd, J = 8.8 and 2.2 Hz, H-3), 8.14 (1H, d, J = 8.9 Hz, H-8), 7.70 (1H, d, J = 8.7 Hz, H-4), 7.21 (1H, d, J = 2.2 Hz, H-5), 7.10 (1H, dd, J = 8.9 and 2.2 Hz, H-7), 4.77 (1H, t, J = 5.7 Hz, O*H*), 4.03 (2H, m, C*H*$_2$OH), 3.95 (3H, *s*, Ar-OC*H*$_3$), 3.49 (1H, m, H-1′), 1.16 ppm (3H, d, J = 6.7 Hz, H-2′); ^{13}C NMR (75.47 MHz,

[D_6]DMSO): δ = 174.9 (C-9), 165.2 (*C*=O, amide), 164.4 (C-6), 157.5 (C-10a), 157.1 (C-4a), 134.0 (C-3), 130.6 (C-2), 127.7 (C-8), 125.3 (C-1), 120.6 (C-9a), 118.0 (C-4), 114.9 (C-8a), 114.0 (C-7), 100.8 (C-5), 64.3 (C-1′), 56.3 (Ar-O*C*H$_3$), 47.5 (*C*H$_2$OH), 17.0 ppm (C-2′); MS (ESI) *m*/*z* (%): 329 [*M*+H]$^+$+1 (25), 328 [*M*+H]$^+$ (100), 255 (79), 233 (45), 197 (4), 155 (12); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11914; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: EtOH/ACN (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

4.4.11. (*R*)-*N*-(2-Hydroxypropyl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (13)

Compound **13** was obtained as a white solid (116 mg, 96%); mp: 208–210 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −81.0 (*c* = 0.74 × 10^{-6} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3440, 3370, 1657, 1612, 1535, 1473, 1446, 1278, 838 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.62 (1H, d, *J* = 2.2 Hz, H-1), 8.30 (1H, dd, *J* = 8.8 and 2.2 Hz, H-3), 8.26 (1H, d, *J* = 8.9 Hz, H-8), 7.54 (1H, d, *J* = 8.8 Hz, H-4), 6.99 (1H, dd, *J* = 8.9 and 2.4 Hz, H-7), 6.92 (1H, d, *J* = 2.4 Hz, H-5), 6.87 (1H, s, N*H*), 4.09 (1H, m, H-2′), 3.96 (3H, s, Ar-OC*H*$_3$), 3.72 (1H, m, H-1′)*, 3.37 (1H, m, H-1′)*, 2.58 (1H, s, O*H*), 1.31 ppm (3H, d, *J* = 6.3 Hz, C*H*$_3$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 175.8 (C-9), 167.0 (*C*=O, amide), 165.5 (C-6), 157.9 (C-10a), 157.0 (C-4a), 134.2 (C-3), 129.8 (C-2), 128.4 (C-8), 124.4 (C-1), 121.1 (C-9a), 118.6 (C-4), 115.5 (C-8a), 113.8 (C-7), 100.4 (C-5), 67.6 (C-2′), 55.9 (Ar-O*C*H$_3$), 47.6 (C-1′), 21.2 ppm (*C*H$_3$); MS (ESI) *m*/*z* (%): 329 [*M*+H]$^+$+1 (19), 328 [*M*+H]$^+$ (100), 282 (9), 218 (75); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11808; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: *n*-hexane/2-PrOH (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.12. (*S*)-*N*-(2-Hydroxypropyl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (14)

Compound **14** was obtained as a white solid (117 mg, 97%); mp: 208–210 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +81.2 (*c* = 0.74 × 10^{-6} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3440, 3371, 1658, 1613, 1534, 1474, 1446, 1277, 837 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.62 (1H, d, *J* = 2.2 Hz, H-1), 8.29 (1H, dd, *J* = 8.8 and 2.2 Hz, H-3), 8.25 (1H, d, *J* = 8.9 Hz, H-8), 7.53 (1H, d, *J* = 8.8 Hz, H-4), 6.99 (1H, dd, *J* = 8.9 and 2.3 Hz, H-7), 6.91 (1H, d, *J* = 2.3 Hz, H-5), 6.87 (1H, s, N*H*), 4.09 (1H, m, H-2′), 3.96 (3H, s, Ar-OC*H*$_3$), 3.72 (1H, m, H-1′)*, 3.37 (1H, m, H-1′)*, 2.58 (1H, s, O*H*), 1.30 ppm (3H, d, *J* = 6.3 Hz, C*H*$_3$); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 174.9 (C-9), 165.3 (*C*=O, amide), 165.1 (C-6), 157.6 (C-10a), 157.2 (C-4a), 133.9 (C-3), 130.5 (C-2), 127.8 (C-8), 125.4 (C-1), 120.7 (C-9a), 118.2 (C-4), 115.0 (C-8a), 114.1 (C-7), 100.8 (C-5), 67.6 (C-2′), 55.9 (Ar-O*C*H$_3$), 47.6 (C-1′), 21.1 ppm (*C*H$_3$); MS (ESI) *m*/*z* (%): 329 [*M*+H]$^+$+1 (19), 328 [*M*+H]$^+$ (74), 255 (100), 233 (53), 197 (6), 155 (13); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11732; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: *n*-hexane/2-PrOH (50:50 v:v), 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.13. *N*-((1*R*,2*S*)-2-Hydroxy-1,2-diphenylethyl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (15)

Compound **15** was obtained as a white solid (162 mg, 94%); mp: 244–246 °C (chloroform/*n*-hexane); $[\alpha]_D^{25°C}$ −181.8 (*c* = 0.33 × 10^{-3} g/mL in chloroform); IR (KBr): $\tilde{\nu}$ 3434, 3341, 1633, 1618, 1528, 1478, 1443, 1266, 834 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 9.00 (1H, d, *J* = 8.9 Hz, N*H*), 8.53 (1H, d, *J* = 2.0 Hz, H-1), 8.13 (1H, d, *J* = 8.8 Hz, H-8), 8.07 (1H, dd, *J* = 8.8 and 2.0 Hz, H-3), 7.64 (1H, d, *J* = 8.8 Hz, H-4), 7.48 (2H, d, *J* = 7.0 Hz, H-2″ and H-6″), 7.46 (2H, d, *J* = 7.0 Hz, H-2‴ and H-6‴), 7.31 (2H, t, *J* = 7.0 Hz, H-3″ and H-5″), 7.28 (2H, t, *J* = 7.0 Hz, H-3‴ and H-5‴), 7.24 (1H, d, *J* = 7.0 Hz, H-4″), 7.19 (1H, d, *J* = 7.0 Hz, H-4‴), 7.19 (1H, d, *J* = 2.3 Hz, H-5), 7.09 (1H, dd, *J* = 8.8 and 2.3 Hz, H-7), 5.48 (1H, d, *J* = 4.9 Hz, O*H*), 5.17 (1H, dd, *J* = 8.9 and 8.7 Hz, H-1′), 4.97 (1H, dd, *J* = 8.7 and 4.9 Hz C*H*OH) 3.94 ppm (3H, s, Ar-OC*H*$_3$); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.7 (C-9), 165.2 (*C*=O, amide), 163.9 (C-6), 157.5 (C-10a), 157.1 (C-4a), 143.6 (C-1″), 141.3 (C-1‴), 133.8 (C-3), 130.4 (C-2), 128.4 (C-3″ and C-5″), 128.4 (C-3‴ and C-5‴),127.6 (C-8), 127.6 (C-2″ and C-6″), 127.1 (C-2‴ and C-6‴), 126.9 (C-4″), 126.7 (C-4‴),125.2 (C-1), 120.6 (C-9a), 118.1 (C-4), 114.9 (C-8a), 114.0 (C-7), 100.8 (C-5), 74.5 (*C*HOH), 59.2 (C-1′), 56.2 ppm (Ar-O*C*H$_3$); MS (ESI) *m*/*z* (%): 467 [*M*+H]$^+$+1 (31), 466 [*M*+H]$^+$ (100), 448 (49), 391 (7), 282 (40), 256 (11); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{29}H_{23}NO_5$: 466.16490, found: 466.16486; ee >97% (HPLC; Column: (*S*,*S*)-Whelk-O1, Mobile phase: ACN/MeOH (50:50 v:v), 1.0 mL/min, λ_{max} 254 nm).

4.4.14. *N*-((1*S*,2*R*)-2-Hydroxy-1,2-diphenylethyl)-6-methoxy-9-oxo-9*H*-xanthene-2-carboxamide (16)

Compound **16** was obtained as a white solid (163 mg, 95%); mp: 243–244 °C (chloroform/*n*-hexane); $[\alpha]_D^{25°C}$ +175.7 (*c* = 0.33 × 10^{-3} g/mL in chloroform); IR (KBr): $\tilde{\nu}$ 3444, 3340, 1636, 1618, 1526, 1478, 1441, 1260, 834 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 9.00 (1H, d, *J* = 8.9 Hz, N*H*), 8.53 (1H, d, *J* = 2.1 Hz, H-1), 8.13 (1H, d, *J* = 8.8 Hz, H-8), 8.07 (1H, dd, *J* = 8.8 and 2.1 Hz, H-3), 7.64 (1H, d, *J* = 8.8 Hz, H-4), 7.48 (2H, d, *J* = 7.0 Hz, H-2″ and H-6″), 7.46 (2H, d, *J* = 7.0 Hz, H-2‴ and H-6‴), 7.31 (2H, t, *J* = 7.0 Hz, H-3″ and H-5″), 7.28 (2H, t, *J* = 7.0 Hz, H-3‴ and H-5‴), 7.24 (1H, d, *J* = 7.0 Hz, H-4″), 7.19 (1H, d, *J* = 7.0 Hz, H-4‴), 7.19 (1H, d, *J* = 2.3 Hz, H-5), 7.09 (1H, dd, *J* = 8.8 and 2.3 Hz, H-7), 5.48 (1H, d, *J* = 4.9 Hz, O*H*), 5.17 (1H, dd, *J* = 8.9 and 8.7 Hz, H-1′), 4.97 (1H, dd, *J* = 8.7 and 4.9 Hz C*H*OH) 3.94 ppm (3H, s, Ar-OC*H*$_3$); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.7 (C-9), 165.2 (*C*=O, amide), 163.9 (C-6), 157.5 (C-10a), 157.1 (C-4a), 143.6 (C-1″), 141.3 (C-1‴), 133.8 (C-3), 130.4 (C-2), 128.4 (C-3″ and C-5″), 128.4 (C-3‴ and C-5‴),127.6 (C-8), 127.6 (C-2″ and C-6″), 127.1 (C-2‴ and C-6‴), 126.9 (C-4″), 126.7 (C-4‴),125.2 (C-1), 120.6 (C-9a), 118.1 (C-4), 114.9 (C-8a), 114.0 (C-7), 100.8 (C-5), 74.5 (*C*HOH), 59.2 (C-1′), 56.2 ppm (Ar-O*C*H$_3$); MS (ESI) *m*/*z* (%): 467 [*M*+H]$^+$+1 (30), 466 [*M*+H]$^+$ (100), 448 (40), 391 (4), 282 (27), 256 (7); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{29}H_{23}NO_5$: 466.16490, found: 466.16495; ee >98% (HPLC; Column: (*S*,*S*)-Whelk-O1, Mobile phase: ACN/MeOH (50:50 v:v), 1.0 mL/min, λ_{max} 254 nm).

4.4.15. (*R*)-*tert*-Butyl 2-(6-methoxy-9-oxo-9*H*-xanthene-2-carboxamido)propanoate (17)

Compound **17** was obtained as a white solid (141 mg, 96%); mp: 160–162 °C (MeOH/water); $[\alpha]_D^{25°C}$ −29.8 (*c* = 0.67 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3389, 1735, 1645, 1622, 1525, 1480, 1458, 826 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.67 (1H, d, *J* = 2.3 Hz, H-1), 8.28 (1H, dd, *J* = 8.8 and 2.3 Hz, H-3), 8.27 (1H, d, *J* = 8.8 Hz, H-8), 7.54 (1H, d, *J* = 8.8 Hz, H-4), 6.99 (1H, dd, *J* = 8.8 and 2.4 Hz, H-7), 6.92 (1H, d, *J* = 2.4 Hz, H-5), 6.91 (1H, d, *J* = 7.2 Hz, N*H*), 4.70 (1H, *quint*, *J* = 7.2 Hz, H-1′), 3.96 (3H, s, Ar-OC*H*$_3$), 1.53 (3H, d, *J* = 7.2 Hz, H-2′), 1.51 ppm (9H, s, (C(C*H*$_3$)$_3$)); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 175.7 (C-9), 172.2 (*C*=O, ester), 165.4 (*C*=O, amide), 165.2 (C-6), 158.0 (C-10a), 157.9 (C-4a), 133.9 (C-3), 129.8 (C-2), 128.4 (C-8), 124.8 (C-1), 121.3 (C-9a), 118.5 (C-4), 115.6 (C-8a), 113.7 (C-7), 100.4 (C-5), 82.3 (C-1′), 55.9 (Ar-OCH$_3$), 49.2 (*C*(CH$_3$)$_3$), 29.7 (C-2′), 28.0 ppm ((*C*H$_3$)$_3$); MS (ESI) *m*/*z* (%): 399 [*M*+H]$^+$+1 (27), 398 [*M*+H]$^+$ (100), 342 (12), 191 (10), 148 (26), 139 (30); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{22}H_{23}NO_6$: 398.15981, found: 398.15952; ee >99% (HPLC;

Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: MeOH, 0.5 mL/min, λ_{max} 254 nm).

4.4.16. (*S*)-*tert*-Butyl 2-(6-methoxy-9-oxo-9*H*-xanthene-2-carboxamido)propanoate (18)

Compound **18** was obtained as a white solid (142 mg, 97%); mp: 160–162 °C (MeOH/water); $[\alpha]_D^{25°C}$ +29.9 ($c = 0.67 \times 10^{-3}$ g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3389, 1735, 1645, 1622, 1525, 1480, 1458, 826 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.67 (1H, d, *J* = 2.3 Hz, H-1), 8.28 (1H, dd, *J* = 8.8 and 2.3 Hz, H-3), 8.27 (1H, d, *J* = 8.8 Hz, H-8), 7.54 (1H, d, *J* = 8.8 Hz, H-4), 6.99 (1H, dd, *J* = 8.8 and 2.4 Hz, H-7), 6.92 (1H, d, *J* = 2.4 Hz, H-5), 6.91 (1H, d, *J* = 7.0 Hz, N*H*), 4.70 (1H, *quint*, *J* = 7.0 Hz, H-1′), 3.96 (3H, s, Ar-OC*H*$_3$), 1.53 (3H, d, *J* = 7.0 Hz, H-2′), 1.51 ppm (9H, s, (C(C*H*$_3$)$_3$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 175.7 (C-9), 172.2 (*C*=O, ester), 165.4 (*C*=O, amide), 165.2 (C-6), 158.0 (C-10a), 157.9 (C-4a), 133.9 (C-3), 129.8 (C-2), 128.4 (C-8), 124.8 (C-1), 121.3 (C-9a), 118.5 (C-4), 115.6 (C-8a), 113.7 (C-7), 100.4 (C-5), 82.3 (C-1′), 55.9 (Ar-O*C*H$_3$), 49.2 (*C*(CH$_3$)$_3$), 29.7 (C-2′), 28.0 ppm ((*C*H$_3$)$_3$); MS (ESI) *m*/*z* (%): 399 [*M*+H]$^+$+1 (25), 398 [*M*+H]$^+$ (100), 342 (11), 191 (20), 148 (84), 139 (6); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{22}H_{23}NO_6$: 398.15981, found: 398.15884; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: MeOH, 0.5 mL/min, λ_{max} 254 nm).

4.4.17. (*R*)-2-((9-Oxo-9*H*-xanthen-3-yl)oxy)-*N*-(1-(*p*-tolyl)ethyl)acetamide (19)

Compound **19** was obtained as a white solid (138 mg, 97%); mp: 172–174 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −15.6 ($c = 5.75 \times 10^{-3}$ g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3286, 1647, 1611, 1549, 1458, 1436, 840 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.63 (1H, d, *J* = 8.6 Hz, N*H*), 8.18 (1H, dd, *J* = 8.0 and 1.7 Hz, H-8), 8.12 (1H, d, *J* = 8.8 Hz, H-1), 7.86 (1H, ddd, *J* = 8.5, 7.1 and 1.7 Hz, H-6), 7.65 (1H, dd, *J* = 8.5 and 1.0 Hz, H-5), 7.48 (1H, ddd, *J* = 8.0, 7.1 and 1.0 Hz, H-7), 7.20 (2H, d, *J* = 8.0 Hz, H-2″ and H-6″), 7.12 (1H, dd, *J* = 8.8 and 2.3 Hz, H-2), 7.08 (1H, d, *J* = 2.3 Hz, H-4), 7.07 (2H, d, *J* = 8.0 Hz, H-3″ and H-5″), 4.98 (1H, m, H-1′), 4.78 (2H, s, OC*H*$_2$), 2.22 (3H, s, Ar-C*H*$_3$), 1.40 ppm (3H, d, *J* = 7.0 Hz, H-2′); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 165.9 (*C*=O, amide), 163.5 (C-3), 157.6 (C-4a), 155.6 (C-10a), 141.2 (C-1″), 135.7 (C-6), 135.2 (C-4″), 128.8 (C-3″ and C-5″), 127.6 (C-1), 126.0 (C-8), 125.9 (C-2″ and C-6″), 124.4 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.3 (C-9a), 114.2 (C-2), 101.5 (C-4), 67.3 (O*C*H$_2$), 47.5 (C-1′), 22.2 (Ar-*C*H$_3$), 20.6 ppm (C-2′); MS (ESI) *m*/*z* (%): 389 [*M*+H]$^+$+1 (29), 388 [*M*+H]$^+$ (100), 349 (3), 270 (8), 149 (13); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{24}H_{21}NO_4$: 388.15490, found: 388.15550; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

4.4.18. (*S*)-2-((9-Oxo-9*H*-xanthen-3-yl)oxy)-*N*-(1-(*p*-tolyl)ethyl)acetamide (20)

Compound **20** was obtained as a white solid (137 mg, 96%); mp: 172–174 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +14.3 ($c = 5.75 \times 10^{-3}$ g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3286, 1647, 1610, 1549, 1457, 1433, 834 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.63 (1H, d, *J* = 8.6 Hz, N*H*), 8.18 (1H, dd, *J* = 8.0 and 1.7 Hz, H-8), 8.12 (1H, d, *J* = 8.8 Hz, H-1), 7.86 (1H, ddd, *J* = 8.5, 7.1 and 1.7 Hz, H-6), 7.65 (1H, dd, *J* = 8.5 and 1.0 Hz, H-5), 7.48 (1H, ddd, *J* = 8.0, 7.1 and 1.0 Hz, H-7), 7.21 (2H, d, *J* = 8.1 Hz, H-2″ and H-6″), 7.12 (1H, dd, *J* = 8.8 and 2.3 Hz, H-2), 7.08 (1H, d, *J* = 2.3 Hz, H-4), 7.07 (2H, d, *J* = 8.1 Hz, H-3″ and H-5″), 4.98 (1H, m, H-1′), 4.78 (2H, s, OC*H*$_2$), 2.22 (3H, s, Ar-C*H*$_3$), 1.40 ppm (3H, d, *J* = 7.0 Hz, H-2′); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 165.9 (*C*=O, amide), 163.4 (C-3), 157.3 (C-4a), 155.6 (C-10a), 141.2 (C-1″), 135.7 (C-6), 135.2 (C-4″), 128.7 (C-3″ and C-5″), 127.6 (C-1), 126.0 (C-8), 125.9 (C-2″ and C-6″), 124.4 (C-7), 121.2 (C-8a), 117.9 (C-5), 115.3 (C-9a), 114.2 (C-2), 101.5 (C-4), 67.3 (O*C*H$_2$), 47.5 (C-1′), 22.1 (Ar-*C*H$_3$), 20.6 ppm (C-2′); MS (ESI) *m*/*z* (%): 389 [*M*+H]$^+$+1 (29), 388 [*M*+H]$^+$ (100), 349 (5), 270 (8), 219 (7), 149 (5); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{24}H_{21}NO_4$: 388.15490, found: 388.15560; ee >98% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

4.4.19. (*R*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (21)

Compound **21** was obtained as a white solid (125 mg, 95%); mp: 184–186 °C (EtOH); $[\alpha]_D^{25°C}$ −8.3 ($c = 1.20 \times 10^{-3}$ g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3412, 3276, 1645, 1614, 1559, 1461, 1438, 1242, 755; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.37 (1H, dd, *J* = 7.6 and 1.6 Hz, H-8), 8.35 (1H, d, *J* = 8.8 Hz, H-1), 7.77 (1H, ddd, *J* = 8.0, 7.5 and 1.6 Hz, H-6), 7.52 (1H, dd, *J* = 8.0 and 0.6 Hz, H-5), 7.44 (1H, ddd, *J* = 7.6, 7.5 and 0.6 Hz, H-7), 7.06 (1H, dd, *J* = 8.8 and 2.4 Hz, H-2), 6.99 (1H, d, *J* = 2.4 Hz, H-4), 6.73 (1H, d, *J* = 8.1 Hz, N*H*), 4.71 (2H, s, OC*H*$_2$), 3.90 (1H, m, H-1′), 3.78 (2H, m, C*H*$_2$OH), 1.97 (1H, m, H-2′), 1.02 (3H, d, *J* = 6.7 Hz, H-3′a)*, 0.97 ppm (3H, d, *J* = 6.7 Hz, H-3′b)*; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.2 (C-9), 167.7 (*C*=O, amide), 162.1 (C-3), 157.8 (C-4a), 156.2 (C-10a), 134.6 (C-6), 128.9 (C-1), 126.7 (C-8), 124.2 (C-7), 121.9 (C-8a), 117.8 (C-5), 116.9 (C-9a), 113.1 (C-2), 101.5 (C-4), 67.5 (O*C*H$_2$), 63.7 (*C*H$_2$OH), 56.9 (C-1′), 28.9 (C-2′), 19.5 (C-3′a)*, 18.7 ppm (C-3′b)*; MS (ESI) *m*/*z* (%): 357 [*M*+H]$^+$+1 (19), 356 [*M*+H]$^+$ (100), 325 (5), 282 (20), 256 (5); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{20}H_{21}NO_5$: 356.14925, found: 356.14918; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: MeOH, 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.20. (*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (22)

Compound **22** was obtained as a white solid (127 mg, 97%); mp: 184–186 °C (EtOH); $[\alpha]_D^{25°C}$ + 8.5 ($c = 1.20 \times 10^{-3}$ g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3407, 3276, 1644, 1613, 1554, 1460, 1438, 1240, 755 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.37 (1H, dd, *J* = 7.6 and 1.6 Hz, H-8), 8.35 (1H, d, *J* = 8.8 Hz, H-1), 7.77 (1H, ddd, *J* = 8.0, 7.5 and 1.6 Hz, H-6), 7.52 (1H, dd, *J* = 8.0 and 0.6 Hz, H-5), 7.44 (1H, ddd, *J* = 7.6, 7.5 and 0.6 Hz, H-7), 7.06 (1H, dd, *J* = 8.8 and 2.4 Hz, H-2), 6.99 (1H, d, *J* = 2.4 Hz, H-4), 6.73 (1H, d, *J* = 8.1 Hz, N*H*), 4.71 (2H, s, OC*H*$_2$), 3.90 (1H, m, H-1′), 3.78 (2H, m, C*H*$_2$OH), 1.98 (1H, m, H-2′), 1.02 (3H, d, *J* = 6.7 Hz, H-3′a)*, 0.98 ppm (3H, d, *J* = 6.7 Hz, H-3′b)*; ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.2 (C-9), 167.7 (*C*=O, amide), 162.1 (C-3), 157.8 (C-4a), 156.2 (C-10a), 134.6 (C-6), 128.9 (C-1), 126.7 (C-8), 124.2 (C-7), 121.9 (C-8a), 117.8 (C-5), 116.9 (C-9a), 113.1 (C-2), 101.5 (C-4), 67.5 (O*C*H$_2$), 63.7 (*C*H$_2$OH), 56.9 (C-1′), 28.9 (C-2′), 19.5 (C-3′a)*, 18.7 ppm (C-3′b)*; MS (ESI) *m*/*z* (%): 357 [*M*+H]$^+$+1 (21), 356 [*M*+H]$^+$ (100), 325 (5), 282 (20), 256 (6); HRMS (ESI) *m*/*z* [*M*+H]$^+$ calcd for $C_{20}H_{21}NO_5$: 356.14925, found: 356.14923; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: MeOH, 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.21. (*R*)-*N*-(1-Hydroxy-4-methylpentan-2-yl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (23)

Compound **23** was obtained as a white solid (134 mg, 98%); mp: 154–156 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +18.0 ($c = 10.00 \times 10^{-3}$ g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3406, 3350–3312,

1652, 1613, 1539, 1461, 1436, 1252, 756 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.20 (1H, dd, J = 8.0 and 1.6 Hz, H-8), 8.13 (1H, d, J = 9.4 Hz, H-1), 7.87 (1H, ddd, J = 8.2, 7.6 and 1.6 Hz, H-6), 7.64 (1H, dd, J = 8.2 and 0.9 Hz, H-5), 7.49 (1H, ddd, J = 8.0, 7.6 and 0.9 Hz, H-7), 7.13 (1H, dd, J = 9.4 and 2.4 Hz, H-2), 7.09 (1H, d, J = 2.4 Hz, H-4), 4.72 (2H, s, OCH_2), 3.90 (1H, m, H-1′), 3.75 (2H, m, CH_2OH), 1.54 (1H, m, H-3′), 1.32 (2H, m, H-2′), 0.84 (3H, d, J = 6.6 Hz, H-4′a)*, 0.81 ppm (3H, d, J = 6.6 Hz, H-4′b)*; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 166.4 (*C*=O, amide), 163.4 (C-3), 157.3 (C-4a), 155.6 (C-10a), 135.2 (C-6), 127.6 (C-1), 125.9 (C-8), 124.4 (C-7), 121.2 (C-8a), 117.9 (C-5), 115.3 (C-9a), 114.2 (C-2), 101.5 (C-4), 67.3 (OCH_2), 63.7 (*C*H_2OH), 48.7 (C-1′), 39.0 (C-2′), 24.2 (C-3′), 23.4 (C-4′a)*, 21.7 ppm (C-4′b)*; MS (ESI) m/z (%): 371 [M+H]$^+$+1 (23), 370 [M+H]$^+$ (100), 328 (30), 282 (23), 256 (6); HRMS (ESI) m/z [M+H]$^+$ calcd $C_{21}H_{23}NO_5$: 370.16490, found: 370.16485; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.22. (*S*)-*N*-(1-Hydroxy-4-methylpentan-2-yl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (24)

Compound **24** was obtained as a white solid (131 mg, 96%); mp: 154–156 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −18.4 (c = 10.00 × 10^{-3}g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3410, 3350–3312, 1654, 1615, 1541, 1462, 1437, 1253, 758 cm^{-1}; ^1H NMR (500.13 MHz, [D_6]DMSO): δ = 8.19 (1H, dd, J = 8.0 and 1.6 Hz, H-8), 8.13 (1H, d, J = 9.4 Hz, H-1), 7.87 (1H, ddd, J = 8.2, 7.6 and 1.6 Hz, H-6), 7.64 (1H, dd, J = 8.2 and 0.9 Hz, H-5), 7.49 (1H, ddd, J = 8.0, 7.6 and 0.9 Hz, H-7), 7.13 (1H, dd, J = 9.4 and 2.4 Hz, H-2), 7.09 (1H, d, J = 2.4 Hz, H-4), 4.71 (2H, s, OCH_2), 3.90 (1H, m, H-1′), 3.78 (2H, m, CH_2OH), 1.55 (1H, m, H-3′), 1.32 (2H, m, H-2′), 0.84 (3H, d, J = 6.6 Hz, H-4′a)*, 0.81 ppm (3H, d, J = 6.6 Hz, H-4′b)*; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 166.4 (*C*=O, amide), 163.4 (C-3), 157.3 (C-4a), 155.6 (C-10a), 135.2 (C-6), 127.6 (C-1), 125.9 (C-8), 124.4 (C-7), 121.2 (C-8a), 117.9 (C-5), 115.3 (C-9a), 114.2 (C-2), 101.5 (C-4), 67.3 (OCH_2), 63.7 (*C*H_2OH), 48.7 (C-1′), 39.0 (C-2′), 24.2 (C-3′), 23.4 (C-4′a)*, 21.7 ppm (C-4′b)*; MS (ESI) m/z (%): 371 [M+H]$^+$+1 (23), 370 [M+H]$^+$ (100), 356 (6), 282 (34), 256 (9), 236 (5); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{21}H_{23}NO_5$: 370.16490, found: 370.16487; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.23. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (25)

Compound **25** was obtained as a white solid (137 mg, 95%); mp: 181–182 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +16.2 (c = 2.90 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3368, 3308, 1659, 1606, 1541, 1451, 1428, 1252, 834 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.61 (1H, d, J = 8.3 Hz, N*H*), 8.19 (1H, dd, J = 7.7 and 1.7 Hz, H-8), 8.13 (1H, d, J = 9.4 Hz, H-1), 7.87 (1H, ddd, J = 8.0, 7.3 and 1.7 Hz, H-6), 7.65 (1H, dd, J = 8.0 and 0.9 Hz, H-5), 7.49 (1H, ddd, J = 7.7, 7.3 and 0.9 Hz, H-7), 7.33 (2H, d, J = 6.7 Hz, H-2″ and H-6″), 7.30(2H, t, J = 6.7 Hz, H-3″ and H-5″), 7.22 (1H, d, J = 6.7 Hz, H-4″), 7.14 (1H, dd, J = 9.4 and 2.3 Hz, H-2), 7.13 (1H, d, J = 2.3 Hz, H-4), 5.02 (1H, t, J = 5.6 Hz, O*H*), 4.93 (1H, m, H-1′), 4.83 (1H, d, J = 14.7 Hz, OCH_2)*, 4.78 (1H, d, J = 14.7 Hz, OCH_2)*, 3.63 ppm (2H, m, CH_2OH); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 166.7 (*C*=O, amide), 163.5 (C-3), 157.4 (C-4a), 155.7 (C-10a), 140.8 (C-1″), 135.3 (C-6), 128.1 (C-3″ and C-5″), 127.7 (C-1), 127.0 (C-2″ and C-6″), 126.9 (C-4″), 126.0 (C-8), 124.5 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.4 (C-9a), 114.2 (C-2), 101.6 (C-4), 67.3 (OCH_2), 64.5 (*C*H_2OH), 55.0 ppm (C-1′); MS (ESI) m/z (%): 391 [M+H]$^+$+1 (23), 390 [M+H]$^+$ (100), 320 (5), 267 (16); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{23}H_{19}NO_5$: 390.13360, found: 390.13370; ee >99% (HPLC; Column: cellulose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: *n*-hexane/EtOH (70:30 v:v), 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.24. (*S*)-*N*-(2-Hydroxy-1-phenylethyl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (26)

Compound **26** was obtained as a white solid (135 mg, 94%); mp: 181–182 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −16.0 (c = 2.90 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3369, 3316, 1667, 1612, 1549, 1461, 1434, 1257, 842 cm^{-1}; ^1H NMR (300.13 MHz, [D_6]DMSO): δ = 8.60 (1H, d, J = 8.4 Hz, N*H*), 8.18 (1H, dd, J = 7.7 and 1.7 Hz, H-8), 8.12 (1H, d, J = 9.5 Hz, H-1), 7.87 (1H, ddd, J = 8.0, 7.3 and 1.7 Hz, H-6), 7.65 (1H, dd, J = 8.0 and 0.9 Hz, H-5), 7.48 (1H, ddd, J = 7.7, 7.3 and 0.9 Hz, H-7), 7.33 (2H, d, J = 6.7 Hz, H-2″ and H-6″), 7.30(2H, t, J = 6.7 Hz, H-3″ and H-5″), 7.22 (1H, d, J = 6.7 Hz, H-4″), 7.14 (1H, dd, J = 9.5 and 2.3 Hz, H-2), 7.13 (1H, d, J = 2.3 Hz, H-4), 4.99 (1H, t, J = 5.6 Hz, O*H*), 4.92 (1H, m, H-1′), 4.84 (1H, d, J = 14.6 Hz, OCH_2)*, 4.77 (1H, d, J = 14.6 Hz, OCH_2)*, 3.63 ppm (2H, m, CH_2OH); ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 174.9 (C-9), 166.6 (*C*=O, amide), 163.5 (C-3), 157.3 (C-4a), 155.6 (C-10a), 140.8 (C-1″), 135.2 (C-6), 128.1 (C-3″ and C-5″), 127.6 (C-1), 127.0 (C-2″ and C-6″), 126.9 (C-4″), 126.0 (C-8), 124.4 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.3 (C-9a), 114.2 (C-2), 101.5 (C-4), 67.3 (OCH_2), 64.5 (*C*H_2OH), 55.0 ppm (C-1′); MS (ESI) m/z (%): 391 [M+H]$^+$+1 (30), 390 [M+H]$^+$ (100), 354 (21), 255 (15), 191 (23), 179 (7); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{23}H_{19}NO_5$: 390.13360, found: 390.13252; ee >99% (HPLC; Column: cellulose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: *n*-hexane/EtOH (70:30 v:v), 0.5 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.25. (*R*)-*N*-(1-Hydroxypropan-2-yl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (27)

Compound **27** was obtained as a white solid (117 mg, 97%); mp: 183–185 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +6.2 (c = 3.33 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3383, 3313, 1650, 1616, 1552, 1460, 1434, 1250, 753 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 8.37 (1H, dd, J = 7.6 and 1.6 Hz, H-8), 8.35 (1H, d, J = 8.8 Hz, H-1), 7.77 (1H, ddd, J = 8.3, 7.5 and 1.6 Hz, H-6), 7.52 (1H, dd, J = 8.3 and 0.8 Hz, H-5), 7.44 (1H, ddd, J = 7.6, 7.5 and 0.8 Hz, H-7), 7.06 (1H, dd, J = 8.8 and 2.4 Hz, H-2), 6.98 (1H, d, J = 2.4 Hz, H-4), 6.73 (1H, d, J = 7.1 Hz, N*H*), 4.67 (2H, s, OCH_2), 4.26 (1H, m, H-1′), 3.73 (2H, m, CH_2OH), 1.31 ppm (3H, d, J = 6.8 Hz, H-2′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.2 (C-9), 167.3 (*C*=O, amide), 162.0 (C-3), 157.8 (C-4a), 156.2 (C-10a), 134.6 (C-6), 128.9 (C-1), 126.7 (C-8), 124.2 (C-7), 121.9 (C-8a), 117.8 (C-5), 116.9 (C-9a), 113.2 (C-2), 101.5 (C-4), 67.4 (OCH_2), 66.6 (C-1′), 47.5 (*C*H_2OH), 17.0 ppm (C-2′); MS (ESI) m/z (%): 329 [M+H]$^+$+1 (19), 328 [M+H]$^+$ (100), 282 (10), 256 (2); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11795; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

4.4.26. (*S*)-*N*-(1-Hydroxypropan-2-yl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (28)

Compound **28** was obtained as a white solid (116 mg, 96%); mp: 182–184 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −6.1 (c = 3.33 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3405, 3313, 1651, 1613, 1541, 1461, 1436, 1252, 755 cm^{-1}; ^1H NMR (300.13 MHz,

$CDCl_3$): δ = 8.38 (1H, dd, J = 7.6 and 1.6 Hz, H-8), 8.35 (1H, d, J = 8.8 Hz, H-1), 7.77 (1H, ddd, J = 8.3, 7.5 and 1.6 Hz, H-6), 7.52 (1H, dd, J = 8.3 and 0.8 Hz, H-5), 7.44 (1H, ddd, J = 7.6, 7.5 and 0.8 Hz, H-7), 7.06 (1H, dd, J = 8.8 and 2.4 Hz, H-2), 6.98 (1H, d, J = 2.4 Hz, H-4), 6.73 (1H, d, J = 7.0 Hz, N*H*), 4.67 (2H, s, OCH_2), 4.26 (1H, m, H-1′), 3.73 (2H, m, CH_2OH), 1.31 ppm (3H, d, J = 6.8 Hz, H-2′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.2 (C-9), 167.3 (*C*=O, amide), 162.0 (C-3), 157.8 (C-4a), 156.2 (C-10a), 134.6 (C-6), 128.9 (C-1), 126.7 (C-8), 124.2 (C-7), 121.9 (C-8a), 117.8 (C-5), 116.9 (C-9a), 113.2 (C-2), 101.5 (C-4), 67.4 (OCH_2), 66.6 (C-1′), 47.5 (*C*H_2OH), 17.0 ppm (C-2′); MS (ESI) m/z (%): 329 [M+H]$^+$+1 (20), 328 [M+H]$^+$ (100), 282 (14), 256 (5); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11791; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

4.4.27. (*R*)-*N*-(2-Hydroxypropyl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (29)

Compound **29** was obtained as a white solid (119 mg, 98%); mp: 161–163 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ −12.8 (c = 3.10 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3440, 3285, 1652, 1611, 1564, 1457, 1319, 1252, 753 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.38 (1H, dd, J = 7.6 and 1.6 Hz, H-8), 8.35 (1H, d, J = 8.8 Hz, H-1), 7.77 (1H, ddd, J = 8.4, 7.5 and 1.6 Hz, H-6), 7.53 (1H, dd, J = 8.4 and 0.6 Hz, H-5), 7.44 (1H, ddd, J = 7.6, 7.5 and 0.6 Hz, H-7), 7.06 (1H, dd, J = 8.8 and 2.4 Hz, H-2), 6.98 (1H, d, J = 2.4 Hz, H-4), 4.70 (2H, s, OCH_2), 4.04 (1H, m, H-2′), 3.64 (1H, m, H-1′)*, 3.27 (1H, m, H-1′)*, 1.28 ppm (3H, d, J = 6.3 Hz, CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.2 (C-9), 167.8 (*C*=O, amide), 162.1 (C-3), 157.8 (C-4a), 156.2 (C-10a), 134.6 (C-6), 128.9 (C-1), 126.7 (C-8), 124.2 (C-7), 121.9 (C-8a), 117.8 (C-5), 116.9 (C-9a), 113.2 (C-2), 101.5 (C-4), 67.4 (OCH_2), 67.3 (C-2′), 46.4 (C-1′), 21.1 ppm (*C*H_3); MS (ESI) m/z (%): 329 [M+H]$^+$+1 (20), 328 [M+H]$^+$ (100), 282 (14), 256 (4); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11794; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

4.4.28. (*S*)-*N*-(2-Hydroxypropyl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (30)

Compound **30** was obtained as a white solid (117 mg, 97%); mp: 161–163 °C (ethyl acetate/*n*-hexane); $[\alpha]_D^{25°C}$ +12.9 (c = 3.10 × 10^{-3} g/mL in dichloromethane); IR (KBr): $\tilde{\nu}$ 3438, 3285, 1658, 1613, 1560, 1458, 1320, 1252, 754 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.38 (1H, dd, J = 7.6 and 1.6 Hz, H-8), 8.35 (1H, d, J = 8.8 Hz, H-1), 7.77 (1H, ddd, J = 8.4, 7.5 and 1.6 Hz, H-6), 7.53 (1H, dd, J = 8.4 and 0.6 Hz, H-5), 7.44 (1H, ddd, J = 7.6, 7.5 and 0.6 Hz, H-7), 7.06 (1H, dd, J = 8.8 and 2.4 Hz, H-2), 6.98 (1H, d, J = 2.4 Hz, H-4), 4.70 (2H, s, OCH_2), 4.04 (1H, m, H-2′), 3.64 (1H, m, H-1′)*, 3.27 (1H, m, H-1′)*, 1.28 ppm (3H, d, J = 6.3 Hz, CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 176.2 (C-9), 167.8 (*C*=O, amide), 162.1 (C-3), 157.8 (C-4a), 156.2 (C-10a), 134.6 (C-6), 128.9 (C-1), 126.7 (C-8), 124.2 (C-7), 121.9 (C-8a), 117.8 (C-5), 116.9 (C-9a), 113.2 (C-2), 101.5 (C-4), 67.4 (OCH_2), 67.3 (C-2′), 46.4 (C-1′), 21.1 ppm (*C*H_3); MS (ESI) m/z (%): 329 [M+H]$^+$+1 (19), 328 [M+H]$^+$ (100), 282 (17), 256 (5); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{18}H_{17}NO_5$: 328.11795, found: 328.11794; ee >99% (HPLC; Column: amylose tris-3,5-dimethylphenylcarbamate coated onto APS-Nucleosil (500 Å, 7 μm, 20% w/w), Mobile phase: ACN, 0.5 mL/min, λ_{max} 254 nm).

4.4.29. *N*-((1*R*,2*S*)-2-Hydroxy-1,2-diphenylethyl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (31)

Compound **31** was obtained as a white solid (163 mg, 95%); mp: 215–218 °C (chloroform/*n*-hexane); $[\alpha]_D^{25°C}$ −66.7 (c = 0.33 × 10^{-3} g/mL in chloroform); IR (KBr): $\tilde{\nu}$ 3412–3190, 3290, 1666, 1617, 1546, 1461, 1441, 1167, 759 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 8.53 (1H, d, J = 8.9 Hz, N*H*), 8.19 (1H, dd, J = 7.9 and 1.5 Hz, H-8), 8.08 (1H, d, J = 8.9 Hz, H-1), 7.88 (1H, ddd, J = 8.5, 7.1 and 1.5 Hz, H-6), 7.65 (1H, dd, J = 8.5 and 0.8 Hz, H-5), 7.49 (1H, ddd, J = 7.9, 7.1 and 0.8 Hz, H-7), 7.19 (10H, m, H-Ar), 6.98 (1H, dd, J = 8.9 and 2.2 Hz, H-2), 6.92 (1H, d, J = 2.2 Hz, H-4), 5.57 (1H d, J = 4.9 Hz, O*H*), 5.01 (1H, dd, J = 8.9 and 6.9 Hz, H-1′), 4.87 (1H, dd, J = 6.9 and 4.9 Hz C*H*OH), 4.66 (1H, d, J = 15.1 Hz, OCH_2)*, 4.61 ppm (1H, d, J = 15.1 Hz, OCH_2)*; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 165.8 (*C*=O, amide), 163.3 (C-3), 157.3 (C-4a), 155.6 (C-10a), 142.8 (C-1″), 140.1 (C-1‴), 135.2 (C-6), 128.3 (C-3″ and C-5″), 128.3 (C-3‴ and C-5‴), 127.6 (C-1), 127.5 (C-2″ and C-6″), 127.0 (C-2‴ and C-6‴), 126.8 (C-4″), 126.7 (C-4‴), 126.0 (C-8), 124.4 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.3 (C-9a), 114.0 (C-2), 101.4 (C-4), 74.4 (*C*HOH), 67.1 (OCH_2), 58.3 ppm (C-1′); MS (ESI) m/z (%): 467 [M+H]$^+$+1 (27), 466 [M+H]$^+$ (83), 448 (100), 304 (22), 282 (31), 256 (8); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{29}H_{23}NO_5$: 466.16490, found: 466.16502; ee >98% (HPLC; Column: (*S*,*S*)-Whelk-O1, Mobile phase: ACN/MeOH (50:50 v:v), 1.0 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.4.30. *N*-((1*S*,2*R*)-2-Hydroxy-1,2-diphenylethyl)-2-((9-oxo-9*H*-xanthen-3-yl)oxy)acetamide (32)

Compound **32** was obtained as a white solid (162 mg, 94%); mp: 216–219 °C (chloroform/*n*-hexane); $[\alpha]_D^{25°C}$ +66.6 (c = 0.33 × 10^{-3} g/mL in chloroform); IR (KBr): $\tilde{\nu}$ 3412–3190, 3290, 1665, 1616, 1545, 1460, 1439, 1165, 759 cm^{-1}; ^{1}H NMR (300.13 MHz, [D_6]DMSO): δ = 8.53 (1H, d, J = 8.9 Hz, N*H*), 8.19 (1H, dd, J = 7.9 and 1.6 Hz, H-8), 8.08 (1H, d, J = 8.9 Hz, H-1), 7.88 (1H, ddd, J = 8.5, 7.1 and 1.6 Hz, H-6), 7.65 (1H, dd, J = 8.5 and 0.9 Hz, H-5), 7.49 (1H, ddd, J = 7.9, 7.1 and 0.9 Hz, H-7), 7.19 (10H, m, H-Ar), 6.98 (1H, dd, J = 8.9 and 2.2 Hz, H-2), 6.92 (1H, d, J = 2.2 Hz, H-4), 5.57 (1H d, J = 4.9 Hz, O*H*), 5.01 (1H, dd, J = 8.9 and 6.9 Hz, H-1′), 4.87 (1H, dd, J = 6.9 and 4.9 Hz C*H*OH), 4.66 (1H, d, J = 15.1 Hz, OCH_2)*, 4.61 ppm (1H, d, J = 15.1 Hz, OCH_2)*; ^{13}C NMR (75.47 MHz, [D_6]DMSO): δ = 175.0 (C-9), 165.8 (*C*=O, amide), 163.3 (C-3), 157.3 (C-4a), 155.6 (C-10a), 142.8 (C-1″), 140.1 (C-1‴), 135.2 (C-6), 128.3 (C-3″ and C-5″), 128.3 (C-3‴ and C-5‴), 127.6 (C-1), 127.5 (C-2″ and C-6″), 127.0 (C-2‴ and C-6‴), 126.8 (C-4″), 126.7 (C-4‴), 126.0 (C-8), 124.4 (C-7), 121.2 (C-8a), 118.0 (C-5), 115.3 (C-9a), 114.0 (C-2), 101.4 (C-4), 74.4 (*C*HOH), 67.1 (OCH_2), 58.3 ppm (C-1′); MS (ESI) m/z (%): 467 [M+H]$^+$+1 (18), 466 [M+H]$^+$ (56), 448 (100), 304 (53), 282 (41), 256 (13); HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{29}H_{23}NO_5$: 466.16490, found: 466.16495; ee >99% (HPLC; Column: (*S*,*S*)-Whelk-O1, Mobile phase: ACN/MeOH (50:50 v:v), 1.0 mL/min, λ_{max} 254 nm).

*Asterisks denote assignments that may be interchanged.

4.5. Biological evaluation

4.5.1. Cell cultures

The three human tumor cell lines, A375-C5 (melanoma), MCF-7 (breast adenocarcinoma), and NCI-H460 (non-small cell lung cancer), were grown as monolayer and routinely maintained in cell culture medium RPMI-1640 (with Glutamax, Lonza) supplemented with 5% heat-inactivated fetal bovine serum (FBS), and incubated in a humidified incubator at 37 °C with 5% CO_2 (Hera Cell, Heraeus). Cell number and viability were routinely determined with Trypan Blue (Sigma) exclusion assay. All experiments were performed with cells in exponential growth with viabilities over 90% and repeated at least three times.

4.5.2. Cell growth assay inhibitory assay

The effects of compounds on the growth of human tumor cell lines were evaluated according to the procedure adopted by the

NCI in the 'In vitro Anticancer Drug Discovery Screen' that uses the protein-binding dye sulforhodamine B (SRB) to assess cell growth.[46] The optimal plating density of each cell line, that ensure exponential growth throughout all the experimental period, was 5×10^5 cells/mL for MCF-7 and NCI-H460 and 7.5×10^5 cells/mL for A375-C5. Cells in 96-well plates were allowed to attach overnight and then exposed for 48 h to five dilutions, starting from maximum concentration of 150 μM. Following this incubation period, the adherent cells were fixed *in situ*, washed and stained with SRB. The bound stain was solubilized and the absorbance was measured at 515 nm in a plate reader (Biotek Synergy 2).

For each tested compound and for each cell line a dose–response curve was obtained and the growth inhibition of 50% (GI_{50}), corresponding to the concentration of compound that inhibited 50% of the net cell growth, was calculated as described.[46] Doxorubicin, used as a positive control, was tested in the same manner. The effect of the vehicle solvent (DMSO) was also evaluated by exposing untreated control cells to the maximum concentration of DMSO used in each assay (0.25%).

4.5.3. Statistical analysis

All experimental data are presented as means ± SEM from at least three independent experiments. The significantly differences between groups were performed with the Graph Pad Prism 4 Software. Statistical significance was assessed by *t*-test considering *p* values <0.05 as statistically significant for a confidence level of 95%.

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