ARTICLE

A synthetically benign one-pot construction of enamino-xanthene dyes†‡

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Polyhydroxylated phenols are components of biomass and precursors of pigments in plants. This paper reports a novel entry to xanthene dyes, involving the reaction of 2,4,6-trihydroxybenzaldehyde with primary aliphatic amines. This catalyst-free synthesis exhibits a high atom economy and can be conducted under eco-friendly conditions and operational simplicity.

Introduction

Phenolic polyols are ubiquitous structures present in cell walls and precursors of heterocyclic pigments and secondary metabolites of plants.[1,2] In particular, 2,4,6-trihydroxybenzaldehyde (THB, **1**) and 2,4,6-trihydroxyacetophenone (THA, **2**) are found in natural products like grandinol (**3** R = H)[3] and eucalrobusones (**3** R=alkyl),[4] being formyl- and acetylphloroglucinol meroterpenoids typical secondary metabolites of *Eucalyptus*[4,5] and *Psidium*[6] genera. Likewise, *O*-glycoside derivatives are common specimens, such as eucalmainoside C **4**, isolated from the fresh fruit of *Eucalyptus maidenii*,[7] **5** from Artemisia stolonifera,[8] **4** and **6** from *Eucalyptus gomphocephala,*[9] **7** from *Lawsonia inermis* and **8** from *Poligonum multiflorum*.[10] In addition, these compounds are precursors of chalcones (such as phloretin, **9**), flavonoids (e.g., lutealin **10** or quercetin **11**), anthocyanidins (cyanidine **12**), and xanthenes (like gentisein **13**), which are generated by enzymatic cyclization steps and provide the bright colors encountered in the plant kingdom.[2]

Xanthene derivatives constitute an important class of naturally-occurring heterocycles, which exhibit a broad range of bioactivity, ranging from antimicrobials to antioxidants.[11] The fluorescent properties of xanthenes make them suitable signaling agents[12] that can be exploited in technological applications such as the preparation of stable laser dyes,[13] fluorescent sensors,[14] protein labeling fluorophores,[15] along with biomolecular imaging[16] and photodynamic therapy (PDT).[17]

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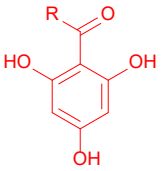
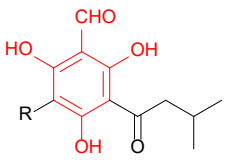
‡Dedicated to the memory of María Dolores Méndez.



1 R=H
2 R=Me



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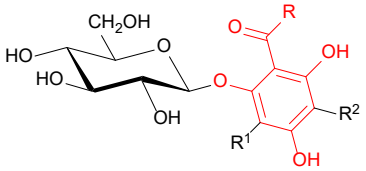
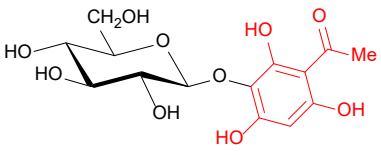


4 R=R$_2$=H, R$_1$=Me
5 R=Me, R$_1$=R^2=H
6 R=R$_1$=Me, R^2=H
7 R=Me, R^1=H, R$_2$=OH



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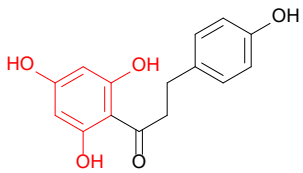

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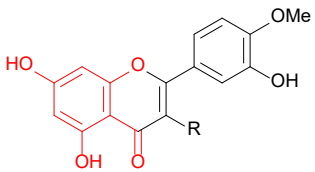
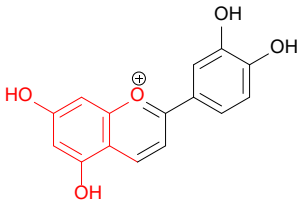


10 R=H
11 R=OH



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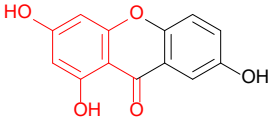

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The latter enables the treatment of several pathologies, and especially diseases associated with abnormal tissue growth, whereby sensitizer-containing drugs are activated by light to kill cancer cells.[18]

The generation of Schiff bases derived from salicylaldehydes and primary amines is well established, and such substances can adopt enoliminic and ketoenamine or zwitterionic forms (Scheme 1). In solution these tautomeric equilibria depend strongly on some structural factors such as substitution pattern and intramolecular hydrogen bonding, and are also markedly influenced by temperature, light and solvent effects.[19] However, Schiff bases of THB with aromatic amines (**14**, R = aryl),[20] hydrazines (**14**, R = NR^1R^2)[21] and hydrazides (**14**, R = COR^1),[22] (thio)semicarbazides (**14**, R = $NHCONH_2$ or $NHCSNH_2$), dithiocarbazides (**14**, R = $NHCSS\text{-}R^1$) and carbohydrazides,[22] show exclusively imine structures in solution.

Results and discussion

To our knowledge no antecedents have been reported on THB-derived Schiff bases with aliphatic primary amines, with the sole exception of the L-arginine Schiff base **15**.[23] Herein we describe a new and environmentally friendly route to xanthene nuclei, which goes beyond the corresponding imine/enamine intermediates leading to a facile assembly of the raw materials.

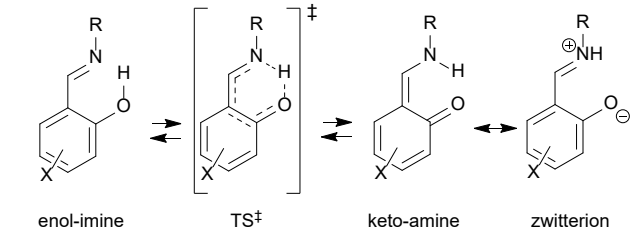
In a preliminary exploration, when the reaction of **1** with an excess of tert-butylamine (1:3 molar ratio) was undertaken in methanol or diethyl ether, a bright yellow solid immediately separated, for which either an imine structure (**14**, R = ^{t}Bu) or alternatively enamine **16**, were tentatively assigned, because the HRMS (ESI$^+$, Fig. S3) showed a m/z peak of 210.1119, consistent with the $[M+H]^+$ ion.

However, NMR spectra evidenced the duplication of *tert*-butyl protons and carbon signals relative to the expected resonances and the IR spectrum shows an intense and complex absorption between 3200-2100 cm^{-1} (ESI$^+$, Fig. S17), characteristic of ammonium salts (**17** or **18**).

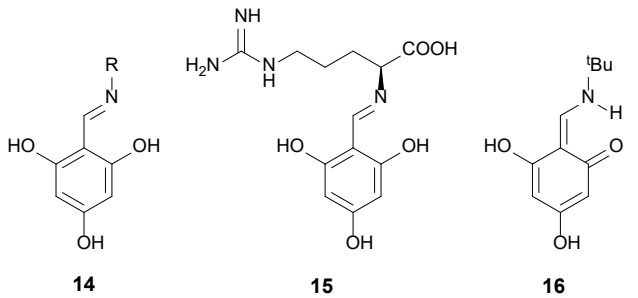
When the condensation was carried out in a 1:1 molar ratio, the reaction mixture darkened rapidly resulting in the formation of an intense red precipitate. At first glance, this might suggest an unwanted side oligomerization. Still, we gave it a chance and pursued further elucidation analyses, which agreed with heterocyclization to compound **19** as the most probable structure (Scheme 2).

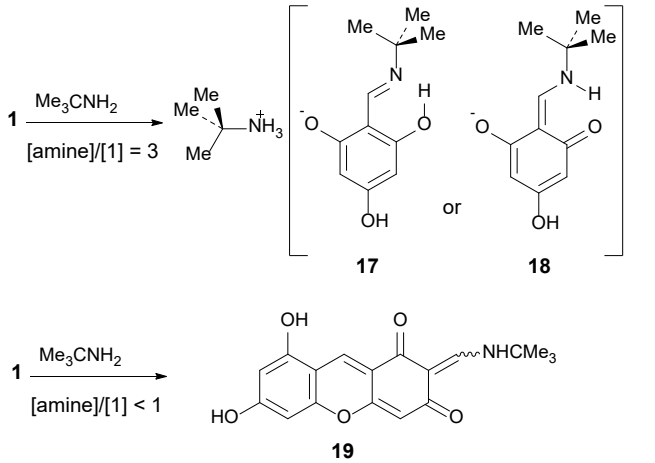
NMR spectra (ESI$^+$, Figs. S33, S34) showed two signal sets, each apparently corresponding to a single product (57:43 ratio), and both should reasonably be isomers owing to the close similarity of chemical shifts, and only one m/z peak at 328.1170 for $[M+H]^+$, consistent with $C_{18}H_{18}NO_5$ (ESI$^+$, Fig. S4). This formula suggests that two molecules of **1** are involved in forming such isomers (2THB + ^{t}BuNH$_2$), which could then be two of keto-enamines **20-22** (signals between 12.5-11.5 ppm are coupled with signals at 8.6-8.3 ppm, $^3J_{NH,CH}$ = 14.5 Hz).

The extensive conjugation would also account for the intense red coloration of the product formed. When NMR spectra were recorded sequentially at higher temperatures, signals collapsed, and their number was reduced by half from 360 K onwards (ESI$^+$, Figs. S61, S62).

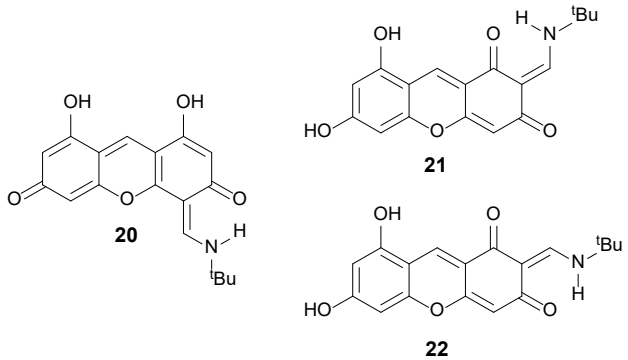


Scheme 1 Tautomeric equilibria for Schiff bases derived from salicylaldehydes.





Scheme 2 Divergent reaction outcomes proposed for the reaction of 2,4,6-trihydroxybenzaldehyde and primary aliphatic amines.



This coalescence indicates the existence of a rapid equilibrium between the two species, a fact that excludes structure **20** from this landscape as it cannot interconvert with either **21** or **22**. Both HSQC and HMBC spectra allowed the full correlation of all protons with their corresponding carbons. The oxygenated substituents are located at positions C1, C3, C6 and C8 in agreement with the initial THB skeleton as depicted in Figure 1. It is worth pointing out that, unlike the present work disclosing the elaboration of xanthene derivatives bearing a substituent at C-2 (an enamino function susceptible of further manipulation), previous syntheses of xanthenes focus almost exclusively on substitution at C-9.[24] Moreover, as documented by recent studies, they are aimed at the development of catalytic systems and/or solvent switching that facilitate the preparation of the xanthene nucleus.[25]

The condensation reaction described for THB and *tert*-butylamine can be extended to other aliphatic primary amines with complete reproducibility (Table 1). Isolated yields (not optimized) ranged from good to excellent and increased significantly when a stoichiometric ratio of the parent reagents was employed (amine/THB, 1:2).

The green pluses associated with this synthesis are noteworthy. Firstly, it involves a sequential assembly of two THB molecules and one amine unit, each releasing one water molecule. As a consequence of this triple dehydration, all carbon atoms are incorporated into the resulting xanthene. In terms of atom economy, the mass of starting materials ending up as product amounts to 86%, while water is the only byproduct accounting for the remaining H and O atoms. All reactions can be conducted at room temperature without extra energy input, and solid products can easily be isolated by filtration. In general, the xanthene derivatives obtained are pure enough and do not require any further chromatographic purification. In addition, such condensations can be conducted in alcoholic or hydroalcoholic (EtOH, MeOH and water) mixtures. Even water alone could be used, although some amines are poorly soluble, which leads to lower yields and complicates unnecessarily the workup protocol.

Furthermore, these compounds, like other xanthene derivatives, show fluorescence behavior, although their optical properties will be reported elsewhere. Thus, fluorescence spectra for xanthene **26** exhibits two emission peaks at λ_{max} 524 and 525 nm (broad bands) after excitation at λ_{max} 324 and 507 nm, respectively. Note the narrow excitation-emission gap in the latter case (figure 2).

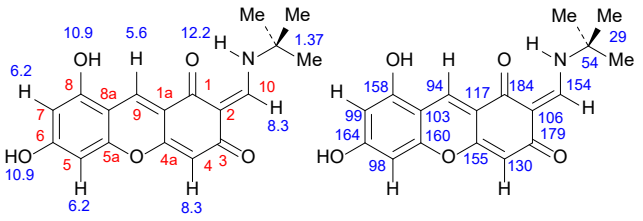
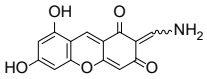
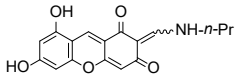
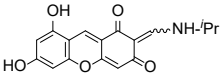
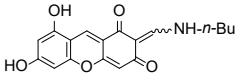
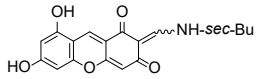
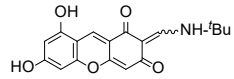
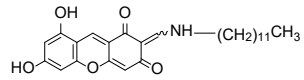
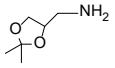
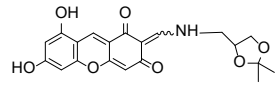
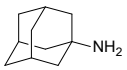
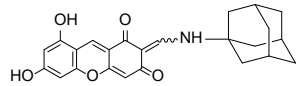
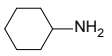
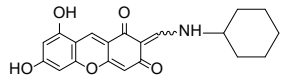
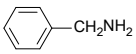
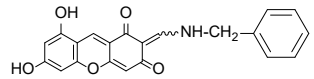
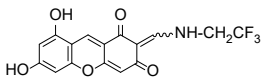


Fig. 1 Numbering (red) and proton/carbon assignment (blue, ppm) for xanthene **21**.

Table 1 Schiff bases **19**, **23-33**, obtained by reaction of THB and primary amines.

Entry	Amine	pK_a[26a]	Product	Yield
1	NH_3	9.21	 **23**	62
2	*n*-Pr-NH_2	10.53	 **24**	80
3	^{i}Pr-NH_2	10.63	 **25**	39
4	*n*-Bu-NH_2	10.59	 **26**	96
5	*sec*-Bu-NH_2	10.56	 **27**	58
6	^{t}Bu-NH_2	10.59	 **19**	94
7	CH_3-$(CH_2)_{11}$-NH_2	10.63	 **28**	49
8		9.16	 **29**	59
9		10.58	 **30**	63
10		10.64	 **31**	60
11		9.34	 **32**	84
12	CF_3CH_2-NH_2	4.7[26b]	 **33**	92

A plausible mechanism explaining the formation of enamino isomers **20-22** could be inferred from structural data, as exemplified for compound **21** in Scheme 3. Tautomers other than those represented cannot be ruled out, nevertheless.

Thus, tautomer **36**, formed by ionization in basic medium (*tert*-butylamine is a strong base, pK_a = 10.55)[26] from enamine **34** (pK_a^{THB} ~7.5), reacts with another molecule of **34** through a formal Mannich, or Michael-type, addition. Similar reactions have been reported, albeit they require metal catalysis.[27] Dimer **38** would evolve with loss of *tert*-butylamine to give **39**, which undergoes cyclization and dehydration leading to **21**.

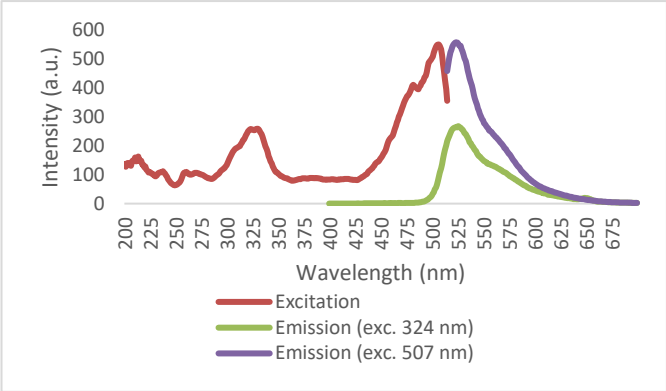
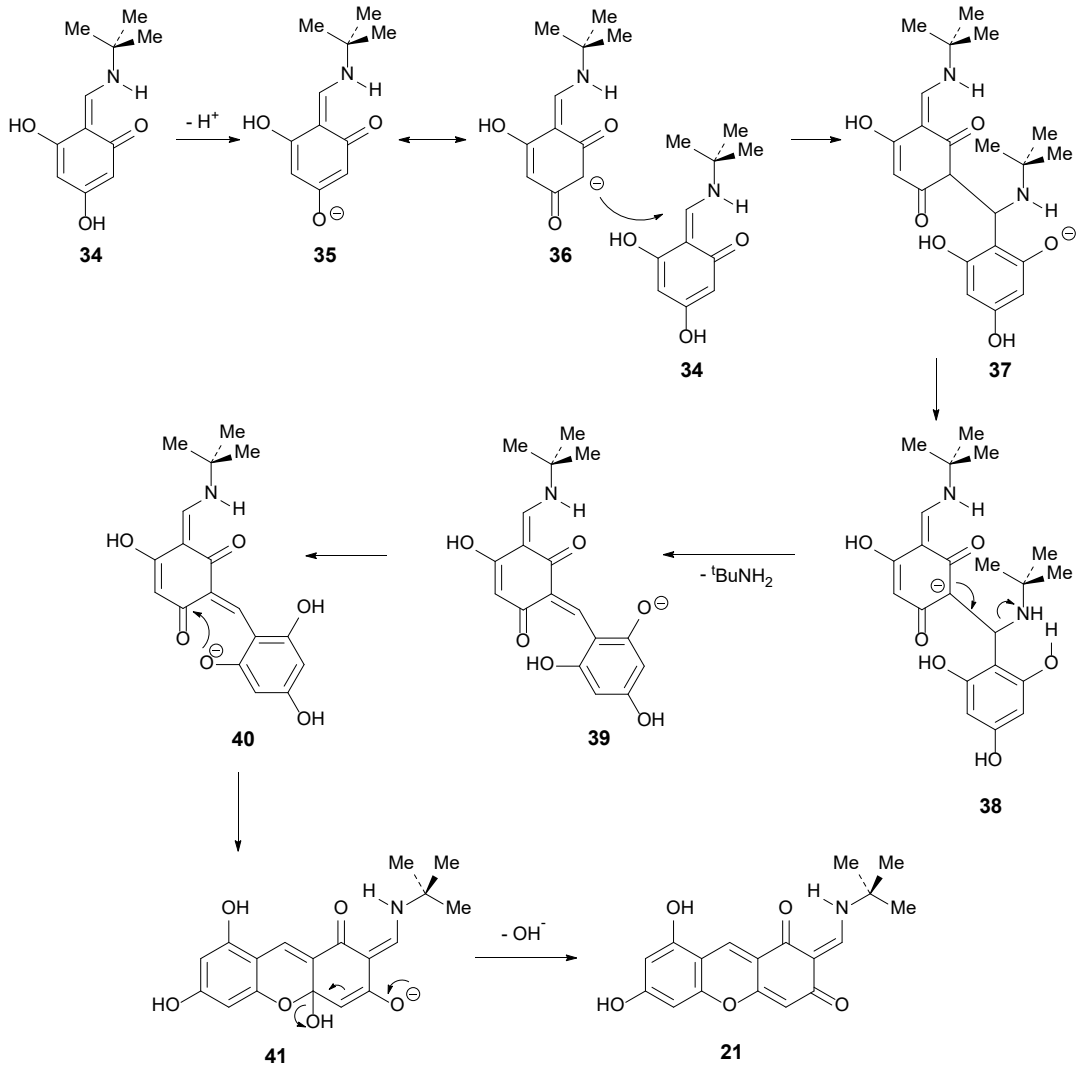


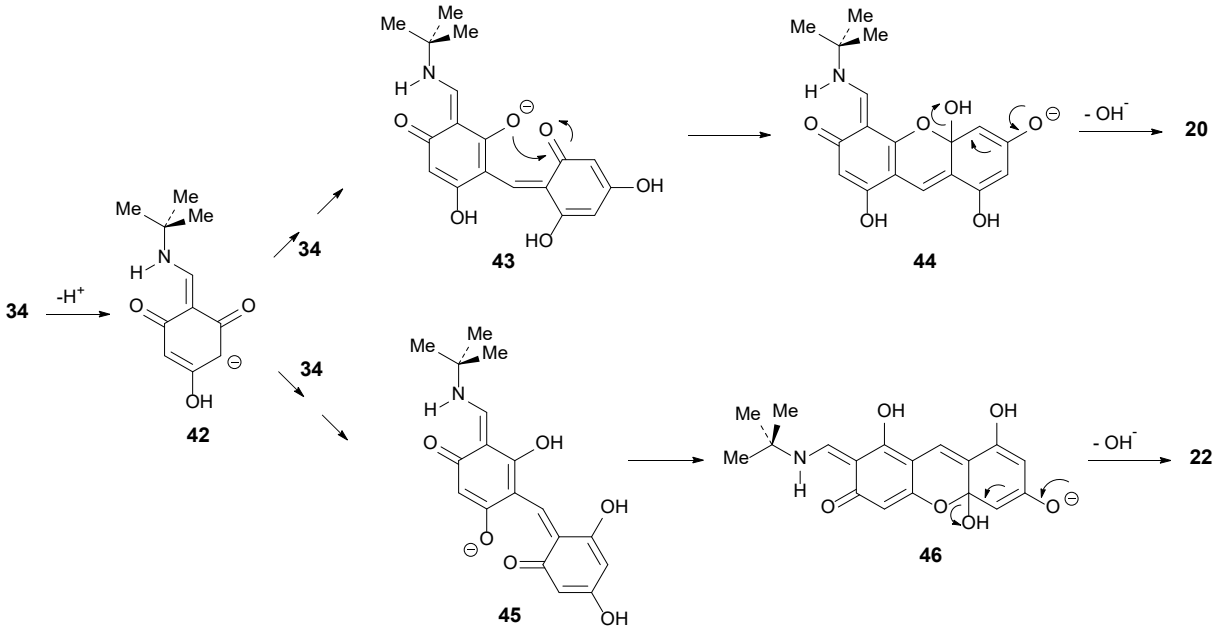
Fig. 2 Top: Fluorescence spectra for xanthene **26**. Excitation and emission spectra were recorded at a concentration of 2 ppm in HPLC-grade methanol. Bottom: (A) solid xanthene **26**; (B) colored solution in MeOH, and (C) sunlight-enhanced fluorescence.

The formation of isomers **20** and **22** should follow a related pathway (Scheme 4). It is worth pointing out that intermediates **39**, **43** and **45** could be interconverted through sequential tautomerizations. Remarkably, the treatment of THB with tertiary amines, such as triethylamine (pKa = 10.8), does not induce its self-condensation to aldehyde **48**, and the red solid lacks the characteristic signals of the xanthene nucleus. Rather, the resulting product shows the typical structural features of an ammonium salt (**47**) (Scheme 5). Consequently, the initial generation of the corresponding Schiff base, and its transformation into an enamine tautomer, appears to be a necessary condition prior to forming the xanthenic core. Variable-temperature experiments made it possible to calculate the energy barrier to E/Z isomerization between **21** and **22**.

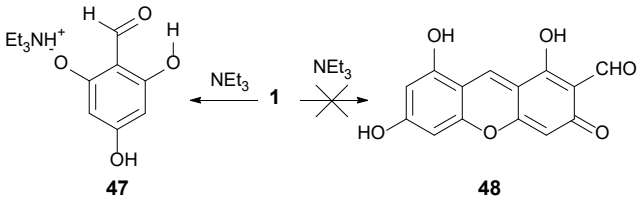
The energy gaps obtained for the coalescence of the different signals lie between 18.1 and 18.7 kcal·mol^{-1} (average value, $\Delta G^{\neq}$ ~18.4 kcal·mol^{-1}) (Table S1). This value is high enough, although it does not impede their slow interconversion at room temperature.



Scheme 3 Proposed self-condensation pathway accounting for the formation of compound **21** featuring a xanthene-derived Schiff base in enamine form.



Scheme 4 Sequential deprotonation and addition pathways proposed for the formation of isomers **20** and **22**.



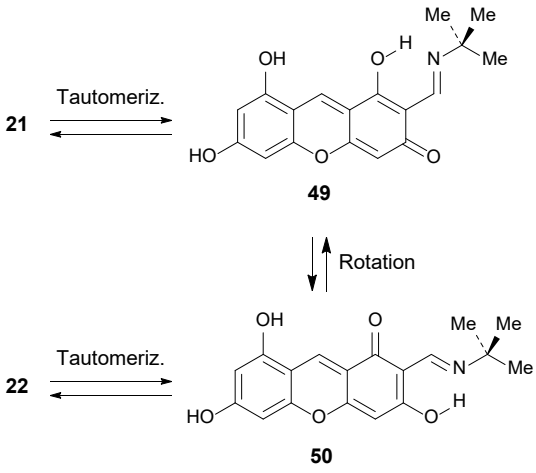
Scheme 5 Proof of concept: imine/enamine formation is compulsory and tertiary aliphatic amines fail to afford the tricyclic system.

This transformation cannot however take place by rotation around the NC=C double bond, which would require a high energy cost, but rather through tautomerization of the enol-imine forms **49/50** (Scheme 6). Moreover, theoretical calculations (ESI$^+$) were conducted on enamines **21/22**, their tautomers **49/50** (Figures S1, S2), and the transition states corresponding to the imine/enamine interconversion, in the gas phase (Figure 3) and taking into account bulk solvation of increasing polarity: ethanol (ε = 24), DMSO (ε = 47), and water (ε = 82) (Tables S3, S4). In all cases, the enamine form becomes significantly more stable than the imine structure, in total agreement with the experimental results. The Gibbs free energy determined for the transition states are slightly lower than those found for the enamine tautomer.

Data collected in Tables S2 and S3 (ESI$^+$) show that the activation free energies are very low (< 6 kcal·mol^{-1}), even negative in the endothermic direction, that is, by moving from enamine to imine forms (-2.0 ≤ ΔG‡ ≤ -0.9 kcal·mol^{-1}).

This result indicates that tautomerization proceeds rapidly, even at very low temperatures. Negative values for the energy barrier (ΔH‡ and ΔG‡) have been described in other intramolecular hydrogen transfers in non-symmetric systems.[28]

Together with tautomerization, enamines **21** and **22** can undergo interconversion, although this process will be occurring slowly at room temperature.



Scheme 6 Mechanism for *E/Z* interconversion of **21** and **22** involving enol-imine tautomers.

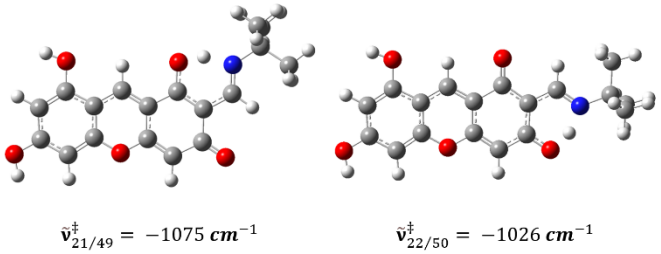


Fig. 3 Transition states and the corresponding imaginary frequencies for the tautomerizations of **21/49** and **22/50**, at the M06-2X/6-311++G(d,p) level in gas phase.

As pointed out above, at 360 K (87 °C) the interconversion becomes so rapid that the signals collapse and are reduced by one half as witnessed by ^{1}H and ^{13}C NMR spectra. A barrier to isomerization of ~18.4 kcal·mol^{-1} (*vide supra*) can be inferred from such dynamic experiments. The calculated thermodynamic parameters for this transformation are shown in Figure 4. Taking into account the differences in stability between each pair **21/49** and **22/50** in DMSO (solvent in which the NMR spectra were recorded), we can write Equation [1]:

$$\Delta G^{\neq}_{isom21\leftrightarrow22} = \Delta G^{\circ}_{21\text{-}22} + \Delta G^{\circ}_{taut21\rightarrow49} + \Delta G^{\neq}_{rot49\leftrightarrow50} = \Delta G^{\neq}_{rot50\leftrightarrow49} + \Delta G^{\circ}_{taut22\rightarrow50} \quad [1]$$

$$\Delta G^{\neq}_{rot49\leftrightarrow50} = \Delta G^{\neq}_{isom21\leftrightarrow22} - \Delta G^{\circ}_{taut21\rightarrow49} - \Delta G^{\circ}_{21\text{-}22} = 18.4 - 6.6 - 0.8 = 11.0 \text{ kcal·mol}^{-1} \quad [2]$$

$$\Delta G^{\neq}_{rot50\leftrightarrow49} = \Delta G^{\neq}_{isom21\leftrightarrow22} - \Delta G^{\circ}_{taut22\rightarrow50} = 18.4 - 6.0 = 12.4 \text{ kcal·mol}^{-1} \quad [3]$$

Therefore, the estimated barrier to interconversion between **49** and **50** should be ~11-12 kcal·mol^{-1}.

On the basis of synthesis and theoretical support, some key ingredients can be extracted. While formation of enamino-xanthenes from THB (pK_a = 7.48) occurs readily with aliphatic primary amines ($pK_a > 8$), it fails with tertiary amines. The same happens with aromatic amines ($pK_a < 6$), for which the reaction is halted in the formation of imine, thereby hampering further self-condensation. The reaction of THB with 4-methoxyaniline (pK_a = 5.29) leading to imine **51** serves as example (91% yield), and in line with previous observations affording imines only (Figs. S16, S55, S56).[20]

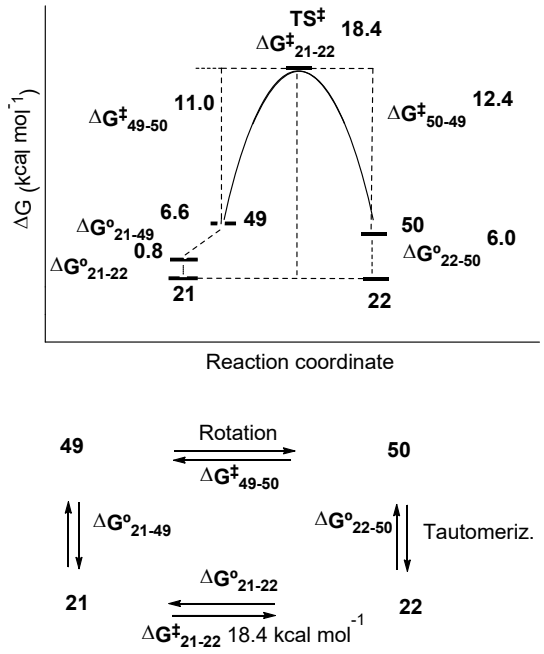
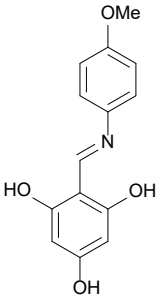
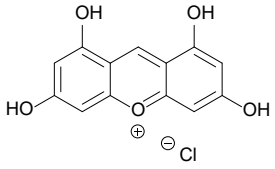


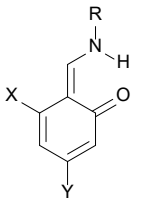
Fig. 4 Thermochemical parameters determined for the interconversion of **21** and **22**.



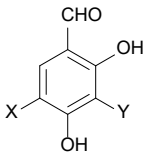
51



52



53 X=H, Y=OH
54 X=OH, Y=H



55 X=Y=H
56 X=H, Y=OH
57 X=OH, Y=H

This distinctive behavior should be ascribed to the different basicity of both types of amines ($\Delta pK_a = pK_a^{alkyl} - pK_a^{arom} \approx 3\text{-}5$). The formation of salt **18** demonstrates the ease of ionization of the Schiff bases derived from THB. A sufficiently basic amine appears to be compulsory to ionize the enamine and cause self-condensation; in fact, aliphatic amines are strong bases ($pK_a \approx 8\text{-}10$). If necessary, this condition is not sufficient, as evidenced by β,β,β-trifluoroethylamine with a pK_a (= 4.7)[26b] comparable to that of anilines, and affording xanthene **33** (Table 1, entry 12). Surprisingly the reaction of THB with arginine leads exclusively to imine **15**,[23] despite the high pK_a values (pK_{a3} = 13.8, side chain group; pK_{a2} = 12.5, α-ammonium ion).[29] Probably the carboxylic group inhibits tautomerization to the enamine form or its ionization and prevents self-condensation. However, the self-condensation of THB under acid catalysis is known to result in the intensely colored xanthylium chloride **52**.[30]

Clearly, the ease of tautomerizing to an enamine structure, as the reactive species indeed, constitutes the other decisive factor for xanthene formation to occur. In previous study, we have shown that the generation of enamines from primary amines is governed by the electronic effect of substituents on the salicylaldehyde ring.[28] Actually, the enamine form of aromatic amines never predominates in solution. The alteration of aromaticity during the tautomeric interconversion between phenol-imine and keto-enamine structures of salicylimines could then justify the abnormal reactivity of the aromatic fragment. Thus, the keto-enamine form is responsible for the room-temperature uncatalyzed H/D exchange (in CD_3OD) at neutral pH and allows electrophilic aromatic substitution to proceed more easily. However, the range of compounds exhibiting facile H/D exchange is limited (**53**, **54**).[31]

This, together with the present self-condensation case, constitute salient examples of anomalous reactivity of aromatic aldehydes. Overall, the substitution pattern is the third essential element and, in fact, we have observed that xanthene

formation does not occur with other hydroxylated salicylaldehydes like **55**,[32] **56** or **57**,[28] while THA gives rise to imine derivatives only.

Conclusions

Summing up, this article describes an unprecedented elaboration of the xanthene nucleus starting from 2,4,6-trihydroxybenzaldehyde and primary amines. The basicity of the latter and the possibility of preferentially forming the enamine tautomer are the driving forces dictating this steric outcome. Furthermore, this chromatography-free and catalyst-free protocol can be regarded as environmentally friendly, working in alcoholic solvents or water, furnishing highly colored and fluorescent products in high yields. We believe this synthetic route provides extra biosynthetic implications, as the pathway to xanthenes and polylignols can be triggered by amino groups of peptide side chains in active sites. Experimental and computational simulations to this end are currently underway.

Experimental section

General methods

Solvent evaporation was carried out in a rotary evaporator at temperatures below 50 °C and estimated pressures between 15-30 mm Hg. Melting points have been determined on a Barnstead Electrothermal 9100 apparatus and are uncorrected. Fluorescence spectra have been recorded on a Varian Cary Eclipse spectrofluorometer with 5 nm excitation and emission slits at 550 V, using methanolic solutions (2 ppm). FT-IR spectra were measured on KBr pellets using a Thermo Electron Corporation IR300 spectrophotometer in the range of 4000 - 400 cm^{-1}, equipped with the EZ OMNIC 6.2 software. HR-MS data have been collected from samples dissolved in DMSO on an Agilent 6520 Accurate-Mass Q-TOF LC/MS system using ESI ionization techniques. NMR spectra were recorded at 298K, on a Bruker Avance III 500 spectrometer (500 MHz and 125 MHz for ^{1}H and ^{13}C nuclei, respectively). Samples were dissolved in 0.6 mL of DMSO-*d6*, using TMS (Me_4Si) as internal standard or the residual peaks for DMSO (^{1}H = 2.500 ppm, ^{13}C = 39.520 ppm) when not clearly identified. The peak patterns are indicated as follows: bs, broad singlet; s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet and m, multiplet. Structural elucidation was achieved through the following one- and bidimensional correlations: DEPT (Distortionless Enhancement by Polarization Transfer); COSY (Proton-proton heteronuclear correlation); HSQC (Heteronuclear Single Quantum Coherence); HMBC (Heteronuclear Multiple Bond Connectivity), and variable-temperature experiments. DFT calculations were performed with Gaussian09 at the M06-2X/6-311++G(d,p) level,[33] using the Solvation Model Based on Density (SMD) for inclusion of solvent effects.[34]

2-[(*tert*-Butylimino)methyl]benzene-1,3,5-triol · *tert*-butylamine (18). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 5.0 mL of absolute ethanol) in an ice bath, 9.0 mmol of *tert*-butylamine were slowly added. The mixture was kept under stirring until the rapid appearance of a yellow precipitate (about three minutes), which was filtered, washed with cold ethanol, and dried under reduced pressure. The product was stored in the refrigerator in the absence of light. The mother liquor was also stored in the refrigerator for 72 hours in the absence of light, to obtain a second fraction (Yield 75%, yellow solid, m.p. 119-120 °C). IR (KBr, ν_{max}/cm^{-1}): 3182, 3027, 2976, 2940, 2881, 2793, 2724, 2605, 2537, 2307, 2229, 2005, 1630, 1552, 1509, 1474, 1429, 1404, 1376, 1322, 1197, 1127, 1073, 883, 821, 691, 680, 565, 510, 466, 440. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm): 9.66 (s, 1H), 5.34 (s, 2H), 1.12 (s, 18H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm): 188.2, 171.8, 167.2, 105.2 (2C), 94.3 (2C), 48.4 (2C), 30.4 (6C). HR-MS $C_{11}H_{15}NO_3$ $[M+H]^+$ m/z calcd. 210.1125, found 210.1119.

(*E* and *Z*)-2-[(tert-Butylamino)methylene]-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (19). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of *tert*-butylamine were slowly added. After stirring for 24 h at room temperature, a red suspension was formed, from which no product could be obtained by filtration. The suspension was evaporated to dryness and the residue was washed successively with cold ethanol and cold methanol. The resulting solid was dried under reduced pressure (Yield 94%, burgundy red powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3046, 2971, 2870, 2607, 1645, 1596, 1483, 1408, 1371, 1308, 1272, 1220, 1163, 1051, 1015, 956, 819, 805, 730, 711, 638, 615, 537, 494, 465. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm): 12.05 (d, *J* = 14.3 Hz, 1H), 12.00 (d, *J* = 14.2 Hz, 1H), 10.89 (bs, 4H), 8.32 (d, *J* = 14.3 Hz, 1H), 8.30 (d, *J* = 14.1 Hz, 1H), 8.18 (s, 1H), 8.16 (s, 1H), 6.22 (d, *J* = 2.6 Hz, 1H), 6.22 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 1.6 Hz, 2H), 5.58 (d, *J* = 1.3 Hz, 1H), 5.53 (d, *J* = 1.1 Hz, 1H), 1.39 (s, 9H, CH_3), 1.36 (s, 9H, CH_3). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm): 186.1, 182.3, 179.3, 177.7, 164.3, 164.2, 159.9, 159.8, 158.0, 157.9, 155.2, 155.1, 154.5, 154.2, 130.7, 129.7, 117.5, 117.4, 106.4, 105.9, 102.7, 102.6, 99.3, 99.1, 98.4, 98.3, 94.4 (2C), 54.5, 54.3, 29.3, 29.0 (4C), 28.9. HR-MS $C_{18}H_{17}NO_5$ $[M+H]^+$ m/z calcd. 328.1180, found 328.1170.

(*E* and *Z*)-2-(Aminomethylene)-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (23). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), a 25% ammonia solution in water was slowly added (1.5 mmol). After 72 h at room temperature, a solid was formed which was filtered, washed successively with cold ethanol, cold acetone, ethyl ether, and dried on silica gel. (Yield 62%, dark brown to blackish solid that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3215, 2974, 1702, 1610, 1448, 1370, 1301, 1262, 1212, 1149, 1060, 1004, 826, 684, 465, 436. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 10.55 (d, *J* = 17.0 Hz, 2H), 10.52 (d, *J* = 15.6 Hz, 2H), 9.32 (s, 2H), 9.18 (s, 2H), 8.18 (d, *J* = 15.9 Hz, 2H), 8.14 (s, 1H), 8.13 (s, 1H), 6.20 (s, 2H), 6.14 (s, 2H), 5.53 (s, 1H), 5.50 (s, 1H). HR-MS $C_{14}H_9NO_5$ $[M+H]^+$ m/z calcd. 272.0554, found 272.0545.

(*E* and *Z*)-6,8-Dihydroxy-2-[(1-propylamino)methylene]-1*H*-xanthene-1,3(2*H*)-dione (24). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of n-propylamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. (Yield 80%, dark orange powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3035, 2961,

2934, 2876, 2618, 1645, 1589, 1557, 1523, 1495, 1467, 1413, 1301, 1264, 1228, 1198, 1165, 1050, 1011, 939, 823, 751, 715, 641, 614, 548, 535, 461. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.48 (dt, *J* = 14.3, 6.3 Hz, 1H), 11.43 (dt, *J* = 13.4, 6.6 Hz, 1H), 10.93 (s, 1H), 10.72 (s, 1H), 8.27 (d, *J* = 14.3 Hz, 1H), 8.26 (d, *J* = 14.1 Hz, 1H), 8.17 (t, *J* = 1.0 Hz, 1H), 8.14 (t, *J* = 1.1 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 2H), 6.18 (d, *J* = 2.0 Hz, 1H), 6.17 (d, *J* = 2.0 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 5.54 (d, *J* = 1.5 Hz, 1H), 3.50 (q, *J* = 6.7 Hz, 2H), 3.46 (q, *J* = 6.7 Hz, 2H), 1.62 (h, *J* = 7.1 Hz, 2H), 1.60 (h, *J* = 7.3 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.7, 182.2, 179.1, 177.7, 164.0, 163.9, 159.7, 159.6, 158.7, 158.6, 157.8, 157.7, 155.0, 154.9, 130.2, 129.2, 117.5, 117.4, 106.4, 106.0, 102.5, 102.4, 99.3, 99.1, 98.2 (2C), 94.2 (2C), 51.1, 50.9, 23.2 (2C), 10.6 (2C). HR-MS $C_{17}H_{15}NO_5$ $[M+H]^+$ m/z calcd. 314.1023, found 314.1033; $[M_2+H]^+$ m/z calcd. 627.1973, found 627.1986; $[M_3+H]^+$ m/z calcd. 940.2923, found 940.2904.

(*E* and *Z*)-6,8-Dihydroxy-2-[(2-propylamino)methylene]-1*H*-xanthene-1,3(2*H*)-dione (25). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 6.0 mL of absolute ethanol), 3.0 mmol of isopropylamine were slowly added. After 72 h at room temperature, a solid was formed which was filtered, washed successively with cold ethanol, cold acetone, ethyl ether, and dried on silica gel. (Yield 39%, burgundy red powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3035, 2971, 2608, 1649, 1590, 1525, 1497, 1468, 1410, 1368, 1327, 1299, 1262, 1230, 1201, 1168, 1052, 1009, 967, 924, 824, 809, 743, 715, 640, 612, 547, 535, 465. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.59 (dd, *J* = 14.3, 7.8 Hz, 1H), 11.53 (dd, *J* = 14.0, 7.6 Hz, 1H), 10.84 (bs, 4H), 8.32 (d, *J* = 14.1 Hz, 1H), 8.31 (d, *J* = 13.9 Hz, 1H), 8.17 (t, *J* = 1.2 Hz, 1H), 8.14 (t, *J* = 1.1 Hz, 1H), 6.21 (d, *J* = 2.1 Hz, 2H), 6.15 (d, *J* = 2.0 Hz, 2H), 5.55 (d, *J* = 1.5 Hz, 1H), 5.52 (d, *J* = 1.5 Hz, 1H), 3.89 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 6H), 1.27 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.8, 182.1, 179.2, 177.7, 164.4, 164.3, 159.8, 159.7, 158.1, 158.0, 156.5, 156.4, 155.0, 154.9, 130.4, 129.4, 117.1 (2C), 106.3, 105.9, 102.5, 102.4, 99.1, 98.9, 98.3, 98.2, 94.1 (2C), 51.2, 51.0, 22.7 (4C). HR-MS $C_{17}H_{15}NO_5$ $[M+H]^+$ m/z calcd. 314.1023, found 314.1029; $[M_2+H]^+$ m/z calcd. 627.1973, found 627.1952.

(*E* and *Z*)-2-[(1-Butylamino)methylene]-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (26). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of n-butylamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. The filtrate was stored in the refrigerator for 72 h leading to a second fraction, which was treated as above. (Yield 96%, orange to burgundy red powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3033, 2950, 2869, 2613, 1644, 1590, 1555, 1519, 1498, 1468, 1445, 1406, 1304, 1269, 1222, 1162, 1051, 1015, 974, 929, 826, 809, 740, 718, 646, 609, 548, 535, 465, 414. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.49 (dt, *J* = 13.6, 6.4 Hz, 1H), 11.45 (dt, *J* = 13.9, 6.8 Hz, 1H), 10.65 (bs, 4H), 8.26 (d, *J* = 14.2 Hz, 1H), 8.25 (d, *J* = 14.0 Hz, 1H), 8.17 (t, *J* = 1.2 Hz, 1H), 8.15 (t, *J* = 1.2 Hz, 1H), 6.22 (d, *J* = 2.1 Hz, 2H), 6.16 (d, *J* = 2.0 Hz, 2H), 5.55 (d, *J* = 1.5 Hz, 1H), 5.52 (d, *J* = 1.4 Hz, 1H), 3.53 (q, *J* = 6.6 Hz, 2H), 3.50 (q, *J* = 6.7 Hz, 2H), 1.59 (p, *J* = 6.9 Hz, 2H), 1.56 (p, *J* = 7.3 Hz, 2H), 1.33 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 1H), 0.91 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.7, 182.2, 179.2, 177.7, 164.2, 164.1, 159.8, 159.7, 158.7, 158.5, 158.1, 157.9, 155.0 (2C), 130.3, 129.3, 117.3 (2C), 106.5, 106.1, 102.5 (2C), 99.2, 99.0, 98.3 (2C), 94.2 (2C), 49.1, 49.0, 31.9 (2C), 19.0 (2C), 13.4 (2C). HR-MS $C_{18}H_{17}NO_5$ $[M+H]^+$ m/z calcd. 328.1180, found 328.1176.

(*E* and *Z*)-2-[(1-Butylamino)methylene]-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (26, multigram procedure). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 g, 19.5 mmol in 12 mL of absolute ethanol), 1.0 mL (9.75 mmol, 0.5 eq.) of n-butylamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. The filtrate was stored in the refrigerator for 72 h leading to a second fraction, which was treated as above. (Yield 85%).

(*E* and *Z*)-2-[(*sec*-Butylamino)methylene]-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (27). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of 2-butylamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. (Yield 58%, dark orange powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3040, 2967, 2931, 2876, 2602, 1642, 1591, 1557, 1525, 1499, 1469, 1410, 1301, 1262, 1230, 1167, 1052, 1011, 949, 829, 809, 747, 715, 641, 614, 564, 535, 482, 465. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.64 – 11.46 (m, 2H), 8.31 (d, *J* = 14.2 Hz, 1H), 8.29 (d, *J* = 13.9 Hz, 1H), 8.18 (s, 1H), 8.16 (s, 1H), 6.21 (s, 2H), 6.15 (s, 2H), 5.56 (s, 1H), 5.52 (s, 1H), 3.64 (m, 2H), 1.59 (m, 4H), 1.26 (t, *J* = 8.6 Hz, 6H), 0.87 (s, 6H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.9, 182.2, 179.4, 177.8, 164.5, 164.4, 159.9(2C), 158.3, 158.1, 157.3, 157.1, 155.1 (2C), 130.6, 129.6, 117.2 (2C), 106.4, 105.9, 102.6 (2C), 99.2, 98.9, 98.4 (2C), 94.2 (2C), 57.1, 57.0, 29.3 (2C), 20.53 (2C), 9.97 (2C). HR-MS $C_{18}H_{17}NO_5$ $[M+H]^+$ m/z calcd. 328.1180, found 328.1182; $[M_2+H]^+$ m/z calcd. 655.2286, found 655.2293.

(*E* and *Z*)-2-[(dodecylamino)methylene]-6,8-dihydroxy-1H-xanthene-1,3(2H)-dione (28). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of dodecylamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. (Yield 59%, burgundy red powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3075, 2923, 2851, 1654, 1590, 1521, 1467, 1446, 1381, 1306, 1209, 1162, 1050, 1021, 976, 831, 756, 720, 645, 612, 532, 460, 413. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.52 – 11.45 (m, 1H), 11.45 – 11.39 (m, 1H), 8.26 (d, *J* = 13.9 Hz, 1H), 8.26 (d, *J* = 13.9 Hz, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 6.22 (s, 2H), 6.16 (s, 2H), 5.54 (s, 1H), 5.52 (s, 1H), 3.54 – 3.45 (m, 4H), 1.56 (bs, 4H), 1.23 (bs, 40H), 0.83 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.8, 182.3, 179.2, 177.7, 164.2, 164.1, 159.8 (2C), 158.7, 158.6, 158.0, 157.9, 155.1, 155.0, 130.3, 129.4, 117.4 (2C), 106.5, 106.1, 102.6, 102.5, 99.3, 99.1, 98.3 (2C), 94.2 (2C), 49.5, 49.4, 31.3, 29.9, 29.0, 28.9 (2C), 28.7, 28.5, 25.8, 22.1, 13.9. HR-MS $C_{26}H_{33}NO_5$ $[M+H]^+$ m/z calcd. 440.2432, found 440.2437; $[M_2+H]^+$ m/z calcd. 879.4790, found 879.4778.

(*E* and *Z*)-2-({[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]amino}methylene)-6,8-dihydroxy-1H-xanthene-1,3(2H)-dione (29). To a solution of 2,4,6-

trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of (2,2-dimethyl-1,3-dioxolan-4-yl)methanamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. (Yield 59%, red powder that decomposes without melting). IR (KBr, ν_{max} /cm^{-1}): 3080, 2984, 2931, 2575, 1639, 1617, 1586, 1523, 1498, 1474, 1445, 1371, 1310, 1265, 1197, 1177, 1159, 1077, 1046, 905, 830, 716, 644, 612, 531, 479, 457. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.48 (dt, *J* = 14.9, 6.8 Hz, 1H), 11.43 (dt, *J* = 13.8, 7.0 Hz, 1H), 10.76 (bs, 4H), 8.27 (d, *J* = 14.1 Hz, 1H), 8.26 (d, *J* = 14.0 Hz, 1H), 8.17 (t, *J* = 1.2 Hz, 1H), 8.16 (t, *J* = 1.2 Hz, 1H), 6.23 (s, 1H), 6.22 (s, 1H), 6.17 (d, *J* = 1.1 Hz, 2H), 6.17 (d, *J* = 0.9 Hz, 1H), 5.56 (d, *J* = 1.5 Hz, 1H), 5.54 (d, *J* = 1.4 Hz, 1H), 4.32 – 4.37 (m, 2H), 4.04 – 4.00 (m, 2H), 3.77 – 3.54 (m, 8H), 1.36 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.8, 182.2, 179.4, 177.8, 164.2, 164.1, 159.9 (2C), 159.7, 159.6, 158.0, 157.8, 155.0 (2C), 130.3, 129.4, 117.3 (2C), 108.8 (2C), 106.8, 106.4, 102.5 (2C), 99.3, 99.1, 98.3, 98.2, 94.2 (2C), 73.9 (2C), 65.4 (2C), 51.4, 51.3, 26.3 (2C), 25.0, 24.0. HR-MS $C_{20}H_{19}NO_7$ [M+H]$^+$ m/z calcd. 386.1234, found 386.11247; [M_2+H]$^+$ m/z calcd. 771.2401, found 771.2415.

(*E* and *Z*)-2-({[(3s,5s,7s)-Adamantan-1-yl]amino}methylene)-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (30). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 6.0 mL of absolute ethanol), 1.5 mmol of 1-adamantylamine were slowly added. After stirring for 14 days at room temperature, a solid was formed which was filtered, washed successively with cold ethanol, ethyl ether, and dried on silica gel. (Yield 63%, burgundy red powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3088, 2907, 2852, 2599, 1636, 1587, 1523, 1474, 1454, 1346, 1292, 1279, 1260, 1183, 1166, 1080, 819, 663, 641, 597, 519, 485, 459, 439. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.99 (d, *J* = 14.3 Hz, 1H), 11.96 (d, *J* = 14.1 Hz, 1H), 8.31 (d, *J* = 14.4 Hz, 1H), 8.29 (d, *J* = 14.2 Hz, 1H), 8.18 (s, 1H), 8.16 (s, 1H), 6.23 (s, 1H), 6.17 (s, 1H), 5.58 (d, *J* = 1.1 Hz, 1H), 5.53 (d, *J* = 2.0 Hz, 1H), 2.17 – 2.08 (m, 6H), 1.89 (d, *J* = 2.9 Hz, 4H), 1.87 (d, *J* = 3.0 Hz, 4H), 1.78 (d, *J* = 2.9 Hz, 4H), 1.67 (d, *J* = 3.3 Hz, 12H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 186.0, 182.2, 179.3, 177.7, 159.9 (2C), 158.1, 157.9, 155.1 (2C), 153.6, 130.7, 129.7, 128.4, 117.4, 117.3, 106.5, 102.6, 99.3, 99.0, 98.4, 94.3, 54.2, 54.0, 51.0, 41.8, 35.1(2C), 28.7, 28.3. HR-MS $C_{24}H_{23}NO_5$ [M+H]$^+$ m/z calcd. 406.1649, found 406.1658; [M_2+H]$^+$ m/z calcd. 811.3225, found 811.3233.

(*E* and *Z*)-2-[(Cyclohexylamino)methylene]-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (31). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of cyclohexylamine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. (Yield 60%, dark red powder that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3093, 3035, 2931, 2855, 2602, 1660, 1644, 1590, 1554, 1524, 1495, 1467, 1402, 1306, 1257, 1225, 1161, 1049, 1017, 968, 936, 921, 889, 828, 751, 717, 642, 612, 591, 531, 466, 422. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.71 (t, *J* = 11.0 Hz, 1H), 11.65 (t, *J* = 10.7 Hz, 1H), 8.32 (d, *J* = 12.2 Hz, 1H), 8.30 (d, *J* = 10.8 Hz, 1H), 8.18 (s, 1H), 8.16 (s, 1H), 6.21 (s, 1H), 6.16 (s, 1H), 5.54 (d, *J* = 18.1 Hz, 2H), 5.56 (s, 1H), 5.52 (s, 1H), 1.89 (s, 4H), 1.69 (d, *J* = 12.3 Hz, 4H), 1.54 (d, *J* = 12.5 Hz, 2H), 1.49 – 1.12 (m, 12H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 186.1, 182.4, 179.4, 177.8, 164.4, 164.3, 160.0, 159.9, 158.2, 158.0, 156.9, 156.8, 155.2, 155.1, 130.7, 129.8, 117.4 (2C), 106.6, 106.1, 102.7 (2C), 99.3, 99.1, 98.5, 98.4, 94.4 (2C), 57.7, 57.6, 32.8, 24.6, 23.9. HR-MS $C_{20}H_{19}NO_5$ [M+H]$^+$ m/z calcd. 354.1336, found 354.1345; [M_2+H]$^+$ m/z calcd. 707.2599, found 707.2619.

(*E* and *Z*)-2-[(Benzylamino)methylene]-6,8-dihydroxy-1*H*-xanthene-1,3(2*H*)-dione (32). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 6.0 mL of absolute ethanol), 1.5 mmol of benzylamine were slowly added. After 72 h at room temperature, a solid was formed which was filtered, washed successively with cold ethanol, cold acetone, ethyl ether, and dried on silica gel. (Yield 84%, orange red powder decomposing without melting). IR (KBr, ν_{max}/cm^{-1}): 3065, 2605, 1645, 1598, 1508, 1438, 1398, 1360, 1298, 1178, 1058, 1024, 826, 752, 733, 696, 656, 634, 594, 534, 463. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.76 – 11.65 (m, 2H), 10.84 (s, 4H), 8.41 (d, *J* = 14.2 Hz, 1H), 8.40 (d, *J* = 13.9 Hz, 1H), 8.17 (t, *J* = 1.2 Hz, 1H), 8.13 (t, *J* = 1.2 Hz, 1H), 7.42 – 7.31 (m, 10H), 6.23 (d, *J* = 2.4 Hz, 1H), 6.23 (d, *J* = 2.4 Hz, 1H), 6.18 (d, *J* = 1.0 Hz, 1H), 6.17 (d, *J* = 1.3 Hz, 1H), 5.57 (d, *J* = 1.4 Hz, 1H), 5.54 (d, *J* = 1.5 Hz, 1H), 4.77 (d, *J* = 6.2 Hz, 2H), 4.74 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 185.8, 182.2, 179.3, 177.8, 164.1, 164.0, 159.9 (2C), 158.7, 158.5, 157.9, 157.8, 155.0, 154.9, 137.3 (2C), 130.3, 129.4, 128.7 (2C), 127.8, 127.7 (2C), 117.3 (2C), 106.8, 106.4, 102.5, 102.4, 99.3, 99.1, 98.2 (2C), 94.2 (2C), 52.5, 52.4. HR-MS $C_{21}H_{15}NO_5$ [M+H]$^+$ m/z calcd. 362.1023, found 362.1031; [M_2+H]$^+$ m/z calcd. 723.1973, found 723.1973.

(*E* and *Z*)-6,8-Dihydroxy-2-{[(2,2,2-trifluoroethyl)amino]methylene}-1*H*-xanthene-1,3(2*H*)-dione (33). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 1.5 mmol of 2,2,2-trifluoroethylamine were slowly added. After stirring for 24 h at room temperature, a red suspension was formed, from which no solid could be separated. The suspension was evaporated to dryness and the residue was washed with cold ethanol. The resulting solid was dried on silica gel. (Yield 92%, dark red to blackish solid that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3064, 3035, 2952, 2864, 2631, 1646, 1595, 1560, 1526, 1507, 1469, 1439, 1420, 1342, 1313, 1287, 1257, 1235, 1169, 1142, 1068, 1052, 1004, 958, 929, 829, 815, 755, 717, 666, 647, 615, 571, 531, 506, 467, 438. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 11.39 (dt, *J* = 14.2, 7.1 Hz, 1H), 11.34 (dt, *J* = 13.4, 7.1 Hz, 1H), 11.05 (s, 2H), 10.85 (s, 2H), 8.37 (d, *J* = 13.6 Hz, 1H), 8.35 (d, *J* = 13.3 Hz, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 6.24 (d, *J* = 2.1 Hz, 2H), 6.19 (d, *J* = 2.4 Hz, 2H), 5.74 (d, *J* = 12.4 Hz, 4H), 5.60 (d, *J* = 1.5 Hz, 1H), 5.58 (d, *J* = 1.5 Hz, 1H). HR-MS $C_{16}H_{10}F_3NO_5$ [M+H]$^+$ m/z calcd. 354.0584, found 354.0600; [M_2+H]$^+$ m/z calcd. 707.1095, found 707.1111.

(*E* and *Z*)-2-{[(4-Methoxyphenyl)imino]methyl}benzene-1,3,5-triol (51). To a solution of 2,4,6-trihydroxybenzaldehyde (3.0 mmol in 2.0 mL of absolute ethanol), 3.0 mmol of *p*-anisidine were slowly added. After stirring for 24 h at room temperature, a solid was formed which was filtered, washed with cold ethanol, and dried under reduced pressure. (Yield 91%, yellow solid that decomposes without melting). IR (KBr, ν_{max}/cm^{-1}): 3404, 2544, 1618, 1569, 1511, 1467, 1398, 1336, 1291, 1251, 1201, 1174, 1153, 1078, 1029, 1003, 924, 892, 812, 748, 666,

621, 575, 505, 481, 453, 431. ^{1}H NMR (DMSO-*d6*, 500 MHz) δ (ppm) 12.24 (bs, 2H), 8.90 (s, 1H), 7.28 – 7.24 (m, 2H), 6.99 – 6.95 (m, 2H), 5.82 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (DMSO-*d6*, 125 MHz) δ (ppm) 163.3, 157.6, 155.8, 141.3, 121.7, 114.6, 101.4, 94.0, 55.2. HR-MS $C_{14}H_{13}NO_4$ $[M+H]^+$ m/z calcd. 260.0917, found 260.0911.

Conflicts of interest

There are no conflicts to declare.

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