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Laboratory note

(2-Arylhydrazonomethyl)-substituted xanthones as antimycotics: synthesis and fungistatic activity against *Candida* species

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Abstract

A series of arylhydrazones derived from various 6,8-diacetoxy- or 6,8-dihydroxy-9-oxo-9*H*-xanthene carboxaldehydes were synthesized and evaluated for their in vitro antifungal properties against two human pathogenic yeasts (*Candida albicans* and *C. krusei*) according to a diffusion method. The activity was strongly dependent from the position of the (1-arylhydrazinyl-2-ylidene)methyl chain in the xanthone molecular skeleton. Compounds having the nitrogen side chain in the 4-position, with a further halogen substitution on the terminal phenyl ring showed fungistatic effects. Within this series, the 4-fluorophenylhydrazinyl derivative **13g** exhibited the highest activity, particularly against *C. krusei*, with a greater efficacy than that of econazole, used as reference. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Arylhydrazono-xanthones; Synthesis; Structural study; In vitro anticandida activity

1. Introduction

Development of fungal infections remains a major therapeutic problem in immunocompromised patients due to AIDS, cancer chemotherapy, or bone marrow transplantation [1,2]. Among the responsible agents of these opportunistic mycoses, *Candida albicans* is predominantly encountered; however other *Candida* species such as *C. krusei* are also emerging as clinically significant pathogens [3–5].

The triazoles (fluconazole and itraconazole) are the most widely used agents for the treatment of fungal infections. However, the emergence of *Candida* resistant species is a crucial and growing problem [6–8]. This resistance may act via various mechanisms (alteration of 14 α-demethylase, defect in Δ 5,6-sterol desaturase) [9,10], but the main pathway seems related to an enhanced drug efflux by ATP binding cassette (ABC) transporters [11]. Furthermore, an increased constitutive expression of the ABC1 transporter gene in *C. krusei* was recently described [12].

During the last years, antifungal drug research mainly focused on the pharmacomodulation of azole compounds. Although numerous derivatives of this class are actually at various stages of development [13],

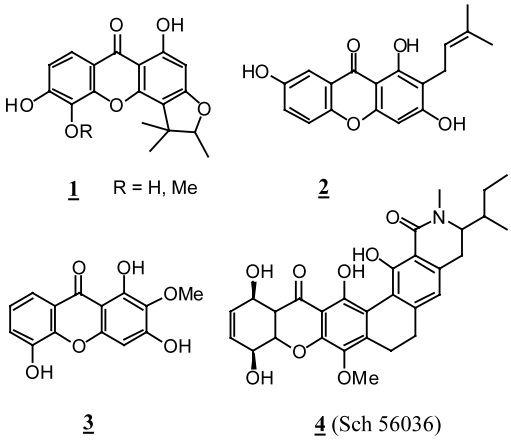

Fig. 1. Some natural xanthones with antifungal activity.

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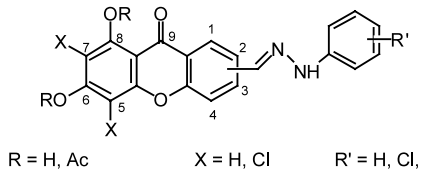


Fig. 2. General structure of the target compounds.

the search for new lead structures, particularly those interacting with novel biological targets, is necessary.

The xanthone nucleus is present in many natural products, including some compounds that have activity against pathogenic fungi [14–17]. These antifungal agents are often characterized either by an acyclic substituent attached to the tricyclic system, or by heterocyclic rings fused to the molecular skeleton (Fig. 1). Compound **4** (Sch 56036) is an example of nitrogen derivative with a strong activity [16].

In addition, various dinitrogen compounds, containing hydrazone or hydrazide subunits in their structure have been reported as interesting fungal growth inhibitors [18–20]. Thus, based on these findings, we have hypothesized in the present work that the combination of a xanthone nucleus with a 1-hydrazinyl-2-ylidene (–NH–N=) side chain might be an intriguing pharmacophore for antifungal drug design. Consequently, different arylhydrazones derived from 9-oxo-9*H*-xanthenecarboxaldehydes were synthesized and evaluated for their in vitro activity against yeasts. In this paper, we mainly focused on the derivatives obtained from 9-oxo-9*H*-xanthene-4-carboxaldehyde, but some isomers in which the hydrazonomethyl chain is attached to position 2 or 3 were also considered, for comparison (Fig. 2).

2. Chemistry

The general synthetic route used for the target xanthones is outlined in Fig. 3.

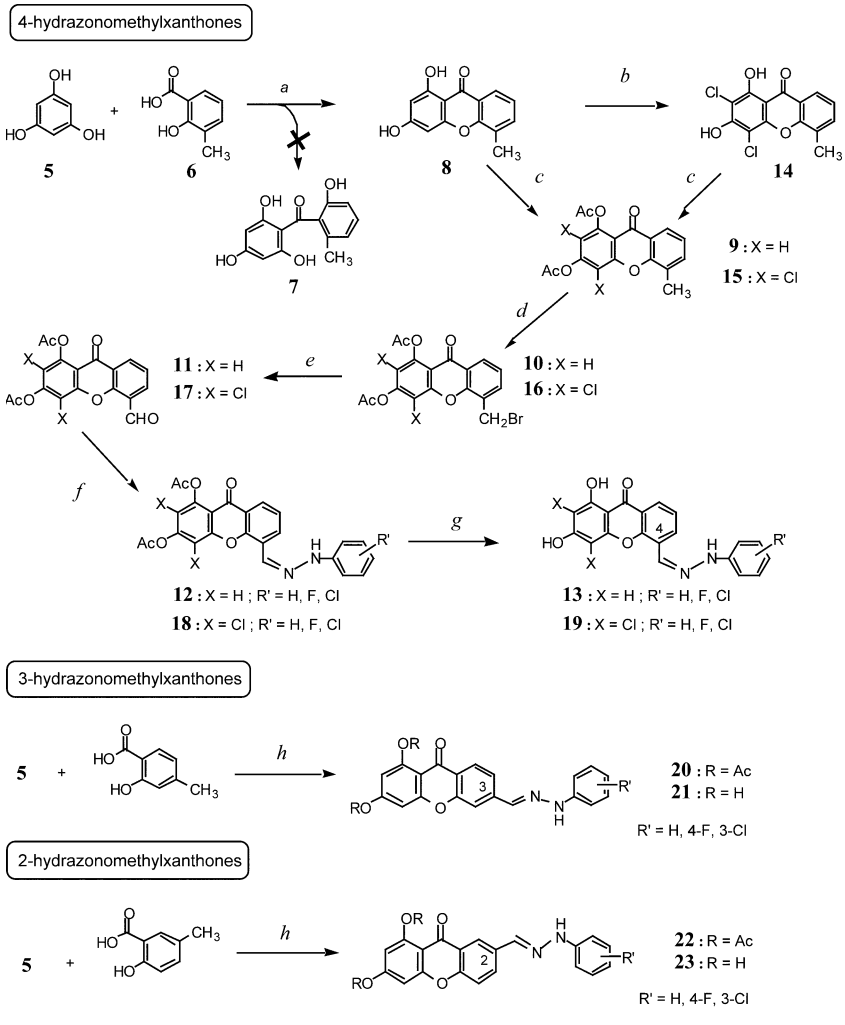


Fig. 3. General synthetic pathway. Reagents: (a) P_2O_5–CH_3SO_3H; (b) SO_2Cl_2/CH_2Cl_2; (c) Ac_2O/pyridine; (d) NBS/DBP/hν; (e) $(Bu_4N)_2Cr_2O_7/CHCl_3$; (f) Ar–NH–NH_2/EtOH; (g) $NaHCO_3/H_2O$; (h) a + c + d + e + f + (g).

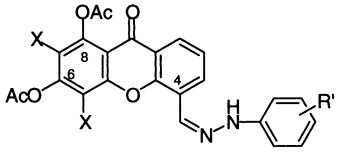
The original procedure for preparing hydroxylated xanthones is the cyclization reaction between phloroglucinols and appropriate substituted salicylic acids, in the presence of a phosphorus oxychloride–zinc chloride as catalyst [21]. Later studies described better results by using a mixture of phosphorus pentoxide–methanesulfonic acid (Eaton's reagent) [22]. For xanthones bearing the nitrogen side chain at position 4, in our experiments, this acylation catalyst was found to be an excellent condensing agent between phloroglucinol (**5**) and 3-methylsalicylic acid (**6**), thus providing high yields of the xanthone **8** and no detectable amounts of the possible benzophenone **7**. The crude product obtained consisted in a mixture of large amount of **8** (average conversion 90–95%) containing a very small amount of starting material and therefore could be used for the next step without any purification. Thus, compound **14** was directly obtained by chlorination of **8** using sulfuryl chloride in dichloromethane.

Synthetic hydroxyxanthones are usually prepared via *O*-benzylated intermediates and subsequent Pd/C catalyzed hydrogenation [23]. However, this protective protocol appeared unsuitable in our synthetic pathway, which required a bromination step. In fact, a competing aromatic halogenation was observed when the benzyloxy analogue of **9** was treated with NBS. Nevertheless, protection of hydroxyl groups as acetyl esters successfully led to the expected bromomethyl derivatives **10** and **16**, respectively.

The carboxaldehydes **11** and **17** were accessible via a controlled oxidation of the bromomethyl precursor with bis tetrabutylammonium dichromate in chloroform. Subsequent reaction with an appropriate arylhydrazine yielded the desired hydrazones **12** or **18**, which upon mild treatment, using a propanol–aqueous sodium hydrogencarbonate, gave the dihydroxyxanthones **13** or **19**. Physical data for the derivatives obtained are given in Tables 1 and 2.

Following a similar procedure, some isomers in which the hydrazonomethyl chain occupies either the position 3 (compounds **20**–**21**, see Table 3) or the position 2 (compounds **22**–**23**, see Table 4) on the xanthone system were prepared from suitable methylsalicylic acids (Fig. 3). The synthesis of these compounds will be reported elsewhere.

Table 1
Physical data for 6,8-diacetoxy-4-(2-arylhydrazonomethyl)xanthones **12** and **18**



No.	X	R′	Method	recrystallization solvent [a]	Yield (%)	Mp (°C)	formula
12a	H	H	A	i	63	196	$C_{24}H_{18}N_2O_6$
12b	H	2-Cl	B	i	86	218	$C_{24}H_{17}ClN_2O_6$
12c	H	3-Cl	A	i	43	220	$C_{24}H_{17}ClN_2O_6$
12d	H	4-Cl	A	i	65	226	$C_{24}H_{17}ClN_2O_6$
12e	H	2-F	D	i	98	198	$C_{24}H_{17}FN_2O_6$
12f	H	3-F	D	i	67	222	$C_{24}H_{17}FN_2O_6$
12g	H	4-F	A	ii	31	200	$C_{24}H_{17}FN_2O_6$
12h	H	2,4-*di*Cl	B	i	80	256	$C_{24}H_{16}Cl_2N_2O_6$
12i	H	2,5-*di*Cl	B	i	90	272	$C_{24}H_{16}Cl_2N_2O_6$
12j	H	2,4-*di*F	B	i	70	216	$C_{24}H_{16}F_2N_2O_6$
18a	Cl	H	E	ii	58	277	$C_{24}H_{16}Cl_2N_2O_6$
18b	Cl	2-Cl	E	iii	67	306	$C_{24}H_{15}Cl_3N_2O_6$
18c	Cl	3-Cl	E	i	72	316	$C_{24}H_{15}Cl_3N_2O_6$
18d	Cl	4-Cl	E	iii	35	260	$C_{24}H_{15}Cl_3N_2O_6$
18e	Cl	2-F	E	iv	91	271	$C_{24}H_{15}Cl_2FN_2O_6$
18f	Cl	3-F	E	iii	37	269	$C_{24}H_{15}Cl_2FN_2O_6$
18g	Cl	4-F	E	ii	75	248	$C_{24}H_{15}Cl_2FN_2O_6$
18h	Cl	2,4-*di*Cl	E	iii	97	274	$C_{24}H_{14}Cl_4N_2O_6$
18i	Cl	2,5-*di*Cl	E	iii	82	279	$C_{24}H_{14}Cl_4N_2O_6$
18j	Cl	2,4-*di*F	E	iii	98	239	$C_{24}H_{14}Cl_2F_2N_2O_6$

[a] i, ethanol; ii, acetone–H_2O; iii, H_2O; iv, ethanol–H_2O; v, acetone.

3. Structural study

Structure of all the prepared compounds was established on the basis of elemental and spectral analyses (IR, NMR and MS), and by comparison with the available literature data.

As an example, spectral data of compound **12a** are presented here while spectral features of other derivatives are given in the experimental part. In the ^{1}H NMR spectrum (Table 5), two singlets respectively at 8.44 ppm (methine proton, –CH=N–) and 10.71 ppm (NH) agreed with the values expected for the protons of a hydrazone group [24]. The aromatic region revealed unambiguous signals for the H5 and H7 atoms (doublets at 7.43 and 7.07 ppm, with a *meta* coupling $J = 2.2$ Hz). On the other hand, ^{13}C NMR chemical shifts were consistent with the abundant reported data on xanthone derivatives [25–30].

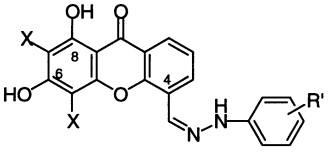
EI–mass spectra of two prototypes **12a** and **12c** confirmed their molecular weights and displayed characteristic fragment ions (protonated ions were often more intense) as shown in Figs. 4 and 5. Initial loss of one cetene molecule (m/z 42) explained the base peaks m/z 388 for **12a** and m/z 422 for **12c** (Fig. 4). The latter ions m/z 198 and 171 (Fig. 5) exhibited the expected fragmentation pattern of a diphenolic xanthone structure [31].

4. Antifungal evaluation and discussion

All final phenolic compounds (**13**, **19**) and their respective acetylated precursors (**12**, **18**) were investigated for their in vitro antifungal activity against two human pathogenic yeasts (*C. albicans*, *C. krusei*) according to an agar diffusion method [32]. In a primary screening assay, compounds have been tested at a fixed amount of 100 μg applied on each test disk.

From the results reported in Table 6, it appears that the unsubstituted phenylhydrazones (‘**a**’ products, in all series) were found to be inactive. On the contrary, derivatives with a monohalogenated phenyl ring showed a significant efficacy (**b**, **c**, and **e**–**g** series) with, in general, a more pronounced activity against *C. krusei* compared to *C. albicans*. Moreover, considering the terminal phenyl ring, dichloro (**h**,**i** series) or difluoro-derivatives (**j** series) unambiguously were less active compared to their monosubstituted analogues. The effect of a chlorine disubstitution on the xanthone system was less clearly established, since quite comparable

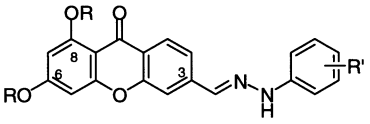
Table 2
Physical data for 6,8-dihydroxy-4-(2-arylhydrazonomethyl)xanthones **13** and **19**



No.	X	R′	Method	Recrystallization solvent [a]	Yield (%)	Mp (°C)	Formula
13a	H	H	A	ii	66	256	$C_{20}H_{14}N_2O_4$
13b	H	2-Cl	C	i	97	257	$C_{20}H_{13}ClN_2O_4$
13c	H	3-Cl	A	ii	56	257	$C_{20}H_{13}ClN_2O_4$
13d	H	4-Cl	A	i	35	236	$C_{20}H_{13}ClN_2O_4$
13e	H	2-F	B	i	87	267	$C_{20}H_{13}FN_2O_4$
13f	H	3-F	B	i	62	262	$C_{20}H_{13}FN_2O_4$
13g	H	4-F	A	i	73	200	$C_{20}H_{13}FN_2O_4$
13h	H	2,4-*di*Cl	B	i	88	311	$C_{20}H_{12}Cl_2N_2O_4$
13i	H	2,5-*di*Cl	B	i	87	328	$C_{20}H_{12}Cl_2N_2O_4$
13j	H	2,4-*di*F	D	i	87	259	$C_{20}H_{12}F_2N_2O_4$
19a	Cl	H	F	ii	87	250	$C_{20}H_{12}Cl_2N_2O_4$
19b	Cl	2-Cl	E	iii	80	300	$C_{20}H_{11}Cl_3N_2O_4$
19c	Cl	3-Cl	E	iv	53	279	$C_{20}H_{11}Cl_3N_2O_4$
19d	Cl	4-Cl	E	iii	95	331	$C_{20}H_{11}Cl_3N_2O_4$
19e	Cl	2-F	E	iii	81	293	$C_{20}H_{11}Cl_2FN_2O_4$
19f	Cl	3-F	E	iii	80	270	$C_{20}H_{11}Cl_2FN_2O_4$
19g	Cl	4-F	E	iii	92	243	$C_{20}H_{11}Cl_2FN_2O_4$
19h	Cl	2,4-*di*Cl	E	iii	91	273	$C_{20}H_{10}Cl_4N_2O_4$
19i	Cl	2,5-*di*Cl	E	iii	99	308	$C_{20}H_{10}Cl_4N_2O_4$
19j	Cl	2,4-*di*F	E	i	88	350	$C_{20}H_{10}Cl_2F_2N_2O_4$

[a] See corresponding footnotes in Table 1.

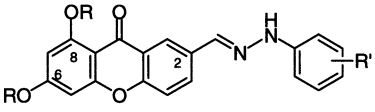
Table 3
Physical data for 3-(2-arylhydrazonomethyl)xanthones **20**–**21**



No.	R	R′	Method	Recrystallization solvent [a]	Yield (%)	Mp (°C)	Formula
20a	Ac	H	A	ii	42	210	$C_{24}H_{18}N_2O_6$
20c	Ac	3-Cl	B	i	88	206	$C_{24}H_{17}ClN_2O_6$
20g	Ac	4-F	B	ii	59	240	$C_{24}H_{17}FN_2O_6$
21a	H	H	E	iv	81	260	$C_{20}H_{14}N_2O_4$
21c	H	3-Cl	E	ii	39	258	$C_{20}H_{13}ClN_2O_4$
21g	H	4-F	E	ii	66	258	$C_{20}H_{13}FN_2O_4$

[a] See corresponding footnotes in Table 1.

Table 4
Physical data for 2-(2-arylhydrazonomethyl)xanthones **22**–**23**



No.	R	R′	Method	Recrystallization solvent [a]	Yield (%)	Mp (°C)	Formula
22a	Ac	H	A	i	61	214	$C_{24}H_{18}N_2O_6$
22c	Ac	3-Cl	A	i	62	219	$C_{24}H_{17}ClN_2O_6$
22g	Ac	4-F	A	v	37	241	$C_{24}H_{17}FN_2O_6$
23a	H	H	E	ii	48	272	$C_{20}H_{14}N_2O_4$
23c	H	3-Cl	E	iv	79	260	$C_{20}H_{13}ClN_2O_4$
23g	H	4-F	E	ii	88	257	$C_{20}H_{13}FN_2O_4$

[a] See corresponding footnotes in Table 1.

levels of efficacy were observed either for dichloroxanthones or the unsubstituted parent compounds: as examples, **13a** (unhalogenated) and **19a** (5,7-dichloro-substituted) were both inactive, whereas **13g** and **19g** displayed a high efficacy.

Thus, the molecular features providing the greatest influence for antifungal properties in this series appeared to be the phenyl substituents in the arylhydrazone unit. The presence of a chlorine at position 2 (compound **12b**) or better at position 3 (compound **12c**) induced a greater activity against *C. krusei* than against *C. albicans*. Noteworthy, compounds carrying a 4-fluoro atom (**13g** and **19g**) were the most potent. However, no clear distinction could be observed in comparing the potency of the 2-fluoro (**13e**) and the 3-fluoro isomers (**13f**) against *C. krusei*. Taken together, these results suggest that factors other than electronic and steric properties of the halogen substituents should be considered to explain the antifungal activity.

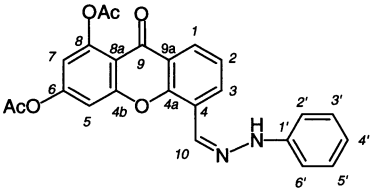
The phenolic OH groups attached in the tricyclic framework also seemed involved in the biological activity profile. Although some acetylated products might substantially inhibit *C. krusei* growth (**12c**, **12g**), the most effective agents were found among the free dihydroxylated derivatives (**13e**–**g**, **19b**,**c**,**f**,**g**,**j**).

In view of the above results, we have further examined the influence of the hydrazonomethyl moiety by varying its position on the xanthone skeleton. Thus, some compounds bearing the side chain at position 2 or 3 have been synthesized and are listed in Tables 3 and 4. Due to inconclusive data previously obtained with 5,7-dichloroxanthones (see discussion above), we omitted to prepare the equivalent molecules in the subsequent series. Strikingly, all of these new compounds derivatives (**j** series) unambiguously were less active compared to their monosubstituted analogues. The effect of a chlorine disubstitution on the xanthone system was less clearly established, since quite comparable were devoid of any antifungal properties against the yeasts tested (Table 6). These findings demonstrate the importance of the nitrogen side chain-positioning, suggesting that the antifungal properties are probably linked to steric factors.

Although an accurate MIC value could not be determined according to a diffusion protocol, we attempted

to compare the anticandida potency of the most interesting derivatives (**13g**, **19g**) to that of econazole, used as reference. Thus, experiments were performed introducing lower amounts (50 μg, then 25 μg) of product, per test disk. Efficacy of the compounds on fungal growth was evaluated by measurement of the inhibited zone size. From the data summarized in Fig. 6, compounds **13g** and **19g** exhibited a different antimycotic profile to that of the chosen reference drug. Against *C. albicans* (Fig. 6a), both compounds **13g** and **19g** showed fungal growth inhibition in a dose-dependent behaviour. However, the most prominent compound, **19g**, resulted less potent than econazole, with an activity level approximately reduced by half. In contrast, the responses observed against *C. krusei* (Fig. 6b) are much more promising. In terms of fungistatic activity, at 50 μg range, **19g** has been found to inhibit the yeast growth more intensely (inhibition zone: ≥ 35 mm) than econazole (inhibition zone: 23 mm). This preliminary study was performed in order to establish the ability to inhibit *Candida* proliferation of our newly synthesized compounds. With the aim of quantifying the efficacy of these derivatives, further antifungal evaluation (i.e. determination of the MIC values by a microdilution test) is in progress.

Table 5
^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) data [a] and main correlations (^{1}H–^{13}C HMBC, and ^{1}H–^{1}H COSY) for compound **12a** [b]



Position	^{1}H	^{13}C	HMBC	COSY
1	8.01 (dd, $^3J = 7.8$, $^4J = 1.4$)	124.7	C1, H3	H1, H2 H1, H3
2	7.46 (t, $^3J = 7.8$)	124.4		H2, H3
3	8.34 (dd, $^3J = 7.6$, $^4J = 1.5$)	129.8	C3, H10	
4		124.9	C4, H10	
4a		151.5	C4a, H10	
4b		156.6	C4b, H5	
5	7.43 (d, $^4J = 2.2$)	108.9		H5, H7
6		154.8		
7	7.07 (d, $^4J = 2.2$)	113.1		
8		150.5	C8a, H5 C8a, H7	
8a		112.0		
9		173.9		
9a		121.8		
10	8.44 (s)	128.7	C10, H3	
C=O (Ac)	–	168.1 and 168.7		
CH_3 (Ac)	2.39 and 2.45	20.8 and 20.9		
NH	10.71 (s)	–		
1′		144.8		
2′	7.14 (d, $^3J = 8.3$)	112.2		H2′, H3′ H2′, H4′
3′	7.26 (t, $^3J = 7.9$)	129.2		H3′, H4′
4′	6.81 (t, $^3J = 7.3$)	119.3		H4′, H5′
5′	7.26 (t, $^3J = 7.9$)	129.2		H5′, H6′
6′	7.14 (d, $^3J = 8.3$)	112.2		H6′, H4′

[a] Chemical shifts, ppm (multiplicity, J in Hz).
[b] In DMSO-d_6 solution.

5. Conclusion

The present study shows that the xanthone framework may be considered as a potential prototype for the synthesis of new antimycotics, unrelated to the classical azole agents. Considering the xanthone nucleus, introduction at position 4 of a hydrazonomethyl chain bearing a fluorophenyl group led to a derivative having in these tests a significantly enhanced activity against *Candida krusei*, by comparison with econazole. These encouraging results against a pathogenic yeast whose incidence is rising, prompt us to further explore this new class of antifungal agents in order to elucidate their mechanism of action.

6. Experimental protocols

6.1. Chemistry

Melting points (m.p.) were obtained using an Electrothermal capillary melting point apparatus (Digital Mel-Temp 3.0, Model 1402) and are uncorrected. Nuclear magnetic resonance spectra were all performed in DMSO-d_6 solution, on a Bruker AMX 500 spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz). Chemical shifts are given as δ units using TMS as an internal standard. Multiplicities in ^{13}C NMR spectra were derived from JMOD experiments. When necessary, 2D experiments (HMQC, HMBC and ^{1}H–^{1}H COSY) were used to assign the signals (for general atom numbering used in description of NMR spectra, see formula included in Table 5). IR spectra were recorded as KBr disks on a Shimadzu IR 470 spectrometer. Positive electronic ionisation mass spectra were obtained on a Fisons autospec (70 eV) spectrophotometer. Analytical thin-layer chro-

Table 6
In vitro growth inhibitory effects [a] of 4-, 3- and 2-(2-arylhydrazonomethyl)xanthones against *C. albicans* [b] and *C. krusei* [c] (diffusion method: 100 μg substance/test disk)

Compound		Acetylated derivatives								Free hydroxylated derivatives							
		12 series		**20** series		**22** series		**18** series		**13** series		**21** series		**23** series		**19** series	
	R′	CA	CK	CA	CK	CA	CK	CA	CK	CA	CK	CA	CK	CA	CK	CA	CK
a	H	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
b	2-Cl	+	++					−	+	−	−					++	+++
c	3-Cl	+	++++	−	−	−	−	+	++	+	+	−	−	−	−	−	+++
d	4-Cl	−	−					−	−	−	+					+	+
e	2-F	+	++					−	+	++	++++					−	+
f	3-F	−	+					−	++	+	++++					−	+++
g	4-F	++	++++	−	−	−	−	+	++	+++	++++	−	−	−	−	++++	++++
h	2,4-*di* Cl	−	−					−	−	+	+					+	+
i	2,5-*di* Cl	−	−					−	−	−	−					−	−
j	2,4-*di* F	−	+					−	++	−	+					−	+++

[a] Size of inhibition zones: (−) 6–7 mm, (+) 8–10 mm, (++) 11–14 mm, (+++) 15–19 mm, (++++) 20 mm and more.
[b] *C. albicans* = CA.
[c] *C. krusei* = CK.

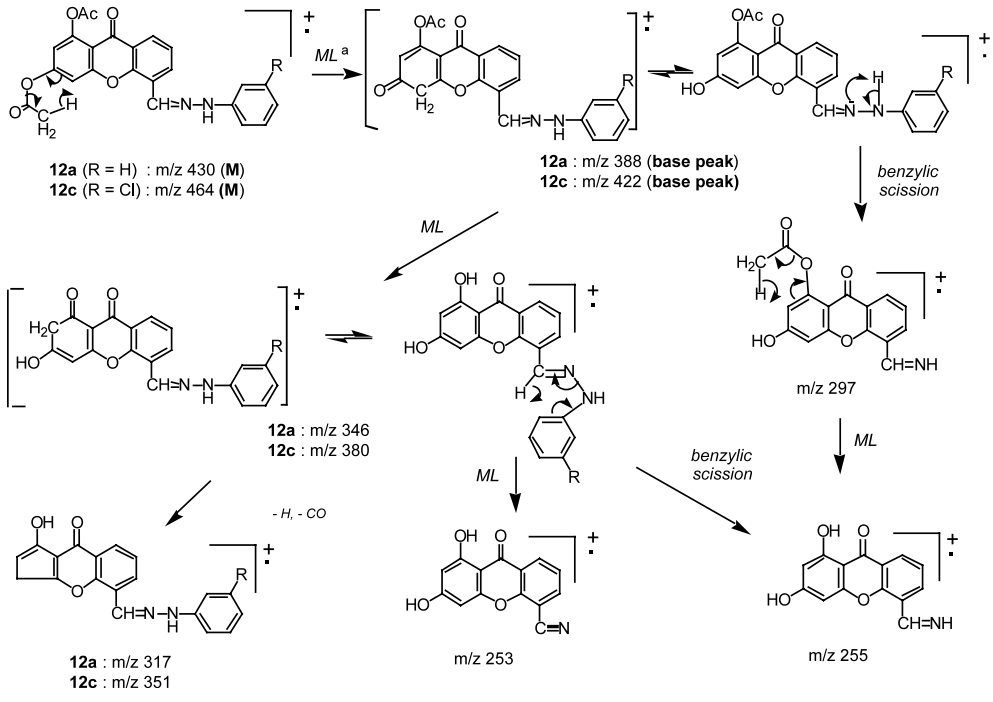


Fig. 4. Mass fragmentation pattern of **12a** and **12c**. [a] *ML* = McLafferty rearrangement.

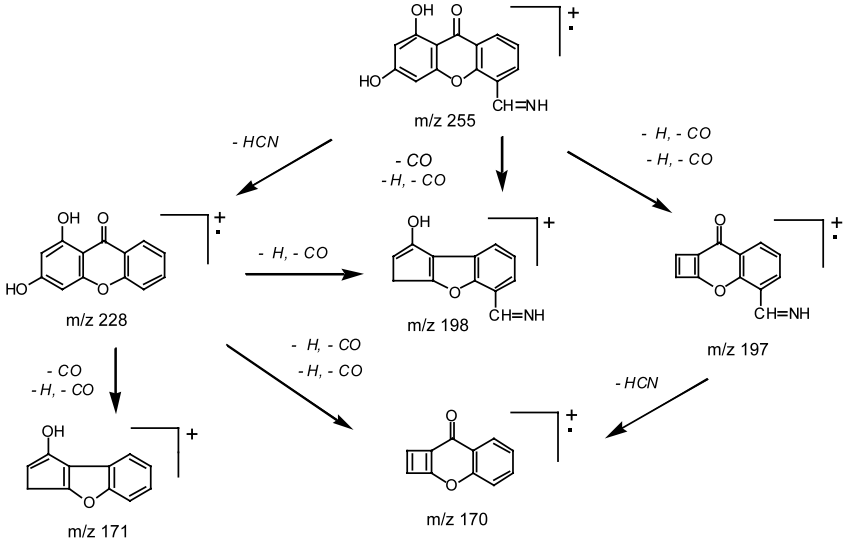


Fig. 5. Mass fragmentation pattern of the xanthone moiety of **12a** and **12c**.

matography (TLC) was performed using aluminium precoated plates (silica gel SDS 60F 254 Whatman, 200 μm thick), and spots were visualized with UV light. Column chromatography was carried out with Merck silica gel, 60–200 μm, according to the flash chromatography technique. Elemental analyses performed on the terminal products were within $\pm 0.4\%$ of the calculated values (for elements indicated in brackets).

6.1.1. 1,3-Dihydroxy-5-methylxanthen-9-one (**8**)

To a mixture of commercially available phloroglucinol dihydrate (9.73 g, 60 mmol), dried at 120 °C overnight, and 3-methylsalicylic acid (9.13 g, 60 mmol) was added slowly 100 mL of Eaton's reagent (P_2O_5–CH_3SO_3H, Aldrich). The mixture was stirred for 20 min at 80 °C, cooled to room temperature (r.t.), and poured onto ice. After vigorous stirring at ambient temperature for 2 h, a thin slurry formed. The solid was collected by filtration, washed with water to adjust the pH to approximately 6, and dried at 60 °C to give **8** as a reddish brown solid (96% yield) which was used without further purification: m.p. 295 °C (lit. [33]); IR (cm^{-1}) 3200 (OH), 1650 (CO), ^1H NMR (δ) 2.35 (s, 3H, CH_3), 6.25 (d, 1H, *H2*, $^4J = 2.2$ Hz), 6.43 (d, 1H, *H4*, $^4J = 2.2$ Hz),

7.10–7.90 (m, 3H, *H6* + *H7* + *H8*), 9.60 (m, 1H, O*H*), 12.90 (m, 1H, O*H*). Anal. $C_{14}H_{10}O_4$ (C, H).

6.1.2. 2,4-Dichloro-1,3-dihydroxy-5-methylxanthen-9-one (**14**)

An amount of 9.45 g (39 mmol) of the xanthone **8** was dissolved in anhydrous dichloromethane (60 mL) and 7.6 mL (93 mmol) of sulfuryl chloride diluted in the same solvent (40 mL) was carefully added. The mixture was stirred at r.t. until all gas release ceased, and then refluxed for 3 h. The reddish solid formed was collected by filtration, washed with water and ethanol to afford crude **14** which was used without any purification: m.p. 250 °C; IR (cm^{-1}) *v* 3300, 3200 (OH), 1640 (CO); ^{1}H NMR (δ) 2.25 (s, 3H, CH_3), 7.15–7.75 (m, 3H, *H6* + *H7* + *H8*), 13.30 (m, 2H, O*H*). Anal. $C_{14}H_8Cl_2O_4$ (C, H, Cl).

6.1.3. 1,3-Diacetoxy-5-methylxanthen-9-ones (**9**, **15**)

A stirred suspension of the dihydroxylated xanthone **8**, or **14** (57.8 mmol) in acetic anhydride (130 mL) and pyridine (10 mL) was warmed under reflux for 3 h, producing a homogeneous dark amber solution. The reaction mixture was allowed to slowly cool to r.t., then poured into ice-water (400 g) and acidified with 12 N hydrochloric acid. The resulting precipitate was separated by filtration and washed with water to pH 7. After drying at 50 °C overnight, the solid was recrystallized from ethanol to afford the required diacetate **9** or **15**.

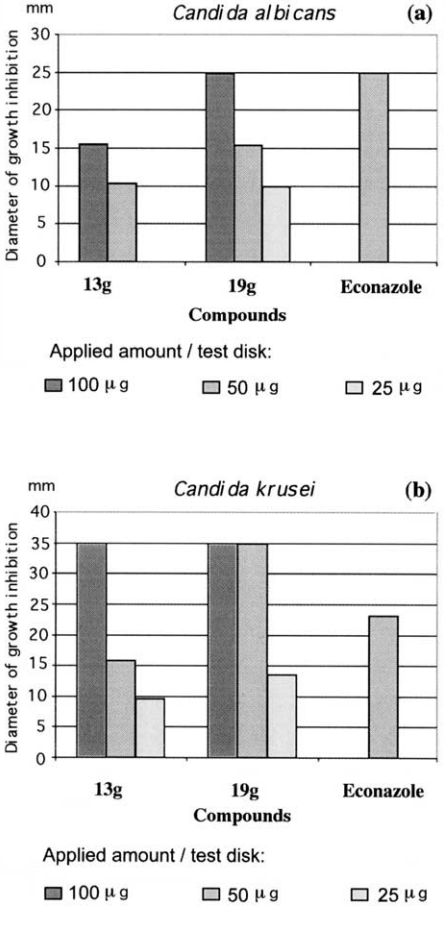


Fig. 6. Inhibitory effects of compounds **13g**, **19g** on the growth of *C. albicans* (a) and *C. krusei* (b) (inhibition zones, in mm; values reported are an average of three independent experiments).

9: m.p. 173 °C (62% yield); IR (cm^{-1}) *v* 1770 (CO ester), 1650 (CO ketone); ^{1}H NMR (δ) 2.34 and 2.39 2[(s, 3H, CO–CH_3)], 2.50 (s, 3H, CH_3), 7.06 (d, 1H, *H2*, $^4J = 1.7$ Hz), 7.36 (t, 1H, *H7*, $^3J = 7.6$ Hz), 7.52 (d, 1H, *H4*, $^4J = 1.3$ Hz), 7.72 (d, 1H, *H6*, $^3J = 7.0$ Hz), 7.95 (d, 1H, *H8*, $^3J = 8.3$ Hz); ^{13}C NMR (δ) 14.9 *C*H_3, 20.8 [2*C*H_3 (Ac)], 109.4 *C4*, 112.0 *C1a*, 113.1 *C2*, 121.2 *C8a*, 123.3 *C7*, 124.0 *C8*, 126.8 *C5*, 136.0 *C6*, 150.3 *C1*, 153.1 *C3*, 154.8 *C5a*, 156.8 *C4a*, 168.2 and 168.6 [2*C*=O (Ac)], 174.3 *C*=O (xanthone). Anal. $C_{18}H_{14}O_6$ (C, H).

15: m.p. 205 °C (40% yield); IR (cm^{-1}) *v* 1780 (CO ester), 1660 (CO ketone); ^{1}H NMR (δ) 2.48 (s, 3H, CH_3), 2.54 and 2.58 [2(s, 3H, CO–CH_3)], 7.29 (t, 1H, *H7*, $^3J = 7.6$ Hz), 7.58 (d, 1H, *H6*, $^3J = 7.2$ Hz), 8.06 (d, 1H, *H8*, $^3J = 7.5$ Hz); ^{13}C NMR (δ) 15.3 *C*H_3, 20.1 and 20.7 [2*C*H_3 (Ac)], 114.3 *C1a*, 116.1 *C4*, 119.0 *C2*, 121.5 *C8a*, 124.1 *C8*, 124.6 *C7*, 127.5 *C5*, 136.3 *C6*, 145.6 *C3*, 148.9 *C1*, 151.3 *C4a*, 153.4 *C5a*, 166.1 and 168.0 [2*C*=O (Ac)], 174.4 *C*=O (xanthone). Anal. $C_{18}H_{12}Cl_2O_6$ (C, H, Cl).

6.1.4. 1,3-Diacetoxy-5-bromomethylxanthen-9-ones (**10**, **16**)

A stirred mixture of the diacetate **9** or **15** (17 mmol), *N*-bromosuccinimide (17 mmol) and dibenzoyl peroxide (0.42 g, 1.7 mmol) in carbon tetrachloride (110 mL) was heated under reflux for 3–5 h under light irradiation (2 × 60 W). The reaction mixture was cooled to 0 °C, stirred for 2 h and filtered. The resulting precipitate was washed successively with water (3 × 15 mL), acetone (2 × 15 mL) and then with diethyl ether to give a yellow solid which was recrystallized from 2-butanone.

10: m.p. 198 °C (50% yield); IR (cm^{-1}) *v* 1780 (CO ester), 1660 (CO ketone); ^{1}H NMR (δ) 2.35 and 2.40 [2(s, 3H, CO–CH_3)], 5.01 (s, 2H, CH_2Br), 7.11 (d, 1H, *H2*, $^4J = 2.3$ Hz), 7.49 (t, 1H, *H7*, $^3J = 7.6$ Hz), 7.59 (d, 1H, *H4*, $^4J = 2.0$ Hz), 8.01 (d, 1H, *H6*, $^3J = 7.3$ Hz), 8.10 (d, 1H, *H8*, $^3J = 8.0$ Hz); ^{13}C NMR (δ) 20.8 [2*C*H_3 (Ac)], 27.0 *C*H_2Br, 109.4 *C4*, 112.1 *C1a*, 113.5 *C2*, 121.6 *C8a*, 126.4 *C7*, 126.7 *C8*, 127.0 *C5*, 136.4 *C6*, 150.4 *C1*, 152.5 *C3*, 155.0 *C5a*, 156.5 *C4a*, 168.2 and 168.6 [2*C*=O (Ac)], 173.7 *C*=O (xanthone). Anal. $C_{18}H_{13}BrO_6$ (C, H).

16: m.p. 184 °C (65% yield); IR (cm^{-1}) *v* 1770 (CO ester), 1660 (CO ketone); ^{1}H NMR (δ) 2.49 and 2.54 [2(s, 3H, CO–CH_3)], 4.82 (s, 2H, CH_2Br), 7.49 (t, 1H,

H7, $^3J = 7.7$ Hz), 7.81 (dd, 1H, *H6*, $^3J = 7.4$ Hz, $^4J =$ 1.6 Hz), 8.20 (dd, 1H, *H8*, $^3J = 8.0$ Hz, $^4J = 1.6$ Hz); ^{13}C NMR (δ) 20.1 and 20.6 [2*C*H$_3$ (Ac)], 25.2 *C*H$_2$Br, 114.4 *C1a*, 116.3 *C4*, 119.6 *C2*, 122.0 *C8a*, 124.9 *C8*, 127.3 *C7*, 127.3 *C5*, 136.2 *C6*, 145.7 *C3*, 149.2 *C1*, 151.1 *C4a*, 152.6 *C5a*, 166.0 and 167.8 [2*C*=O (Ac)], 173.7 *C*=O (xanthone). Anal. $C_{18}H_{11}BrCl_2O_6$ (C, H, Cl).

6.1.5. General procedure for the preparation of 6,8-diacetoxy-9-oxo-9H-xanthene-4-carboxaldehyde **11** *and 6,8-diacetoxy-5,7-dichloro-9-oxo-9H-xanthene-4-carboxaldehyde* **17**

To a solution of bis-tetrabutylammonium dichromate (10 mmol) obtained as previously described [34] in chloroform (100 mL), 5 mmol of bromomethyl derivative **10** or **16** was added. The reaction mixture was heated under reflux for 5 h. After cooling to r.t., the resulting inorganic precipitate was removed by trituration with 20 g of silica gel (40–63 μm), filtration, and washing twice with 50 mL of ethyl acetate. The combined organic layers were concentrated under reduced pressure to afford a greenish brown-coloured oil. The product was dissolved in dichloromethane (5 mL) and further purified on silica gel column (63–200 μm) eluting with dichloromethane–ethyl acetate (9:1) to give the expected carboxaldehyde. Analytically pure sample was obtained by crystallization from ethanol.

11: yellowish white crystals m.p. 172 °C (29% yield); IR (cm^{-1}) *v* 1770 (CO ester), 1690 (CO aldehyde), 1660 (CO ketone); ^{1}H NMR (δ) 2.36 and 2.40 [2(s, 3H, CO–C*H*$_3$)], 7.13 (d, 1H, *H2*, $^4J = 2.0$ Hz), 7.60 (t, 1H, *H7*, $^3J = 7.6$ Hz), 7.61 (d, 1H, *H4*, $^4J = 2.4$ Hz), 8.25 (d, 1H, *H6*, $^3J = 7.6$ Hz), 8.39 (d, 1H, *H8*, $^3J = 8.0$ Hz), 10.67 (s, 1H, C*H*O); ^{13}C NMR (δ) 21.7 and 21.8 [2C*H*$_3$ (Ac)], 110.6 *C5*, 113.3 *C8a*, 114.8 *C7*, 123.1 *C1a*, 125.4 *C2*, 125.4 *C4*, 133.0 *C1*, 135.2 *C3*, 151.3 *C8*, 156.1 *C6*, 156.4 *C4a*, 157.5 *C5a*, 169.1 and 169.6 [2*C*=O (Ac)], 174.4 *C*=O (xanthone), 188.8 *C*HO. Anal. $C_{18}H_{12}O_7$ (C, H).

17: m.p. 215 °C (26% yield); IR (cm^{-1}) *v* 1780 (CO ester), 1700 (CO aldehyde), 1660 (CO ketone); ^{1}H NMR (δ) 2.49 and 2.54 [2(s, 3H, CO–C*H*$_3$)], 7.68 (t, 1H, *H7*, $^3J = 7.7$ Hz), 8.32 (dd, 1H, *H6*, $^3J = 7.3$ Hz, $^4J = 1.7$ Hz), 8.43 (dd, 1H, *H8*, $^3J = 7.9$ Hz, $^4J = 1.9$ Hz), 10.69 (s, 1H, C*H*O); ^{13}C NMR (δ) 20.8 and 21.3 [2*C*H$_3$ (Ac)], 115.3 *C8a*, 116.5 *C5*, 119.5 *C7*, 122.7 *C1a*, 125.7 *C4*, 126.2 *C2*, 133.0 *C1*, 135.6 *C3*, 149.4 *C8*, 145.9 *C6*, 151.7 *C5a*, 156.0 *C4a*, 167.5 and 168.5 [2*C*=O (Ac)], 173.8 *C*=O (xanthone), 187.9 *C*HO. Anal. $C_{18}H_{10}Cl_2O_7$ (C, H, Cl).

*6.1.6. General procedure for the preparation of hydrazones (***12***,* **18***)*

6.1.6.1. Method A. A suspension of **11** or **17** (1 mmol) and the appropriate arylhydrazine (1.2 mmol) in 15 mL of 1-propanol was stirred at r.t. for 15 min, and then acetic acid (about 0.5 mL) was added dropwise. The suspension was stirred for additional 15 min at r.t. and then heated under reflux for 2 h. The mixture was cooled to r.t. and filtered to give the desired hydrazone **12** or **18**.

6.1.6.2. Method B. To a suspension of carboxaldehyde **11** or **17** (2 mmol) and arylhydrazine (2.2 mmol) in ethanol (40 mL), acetic acid (1 mL) was slowly added. The mixture was then refluxed for 30 min, cooled to r.t. and the resulting precipitate was collected by filtration and purified by crystallization.

6.1.6.3. Method C. A stirred mixture of carboxaldehyde **11** or **17** (1 mmol) and a slight excess of the appropriate arylhydrazine (1.2 mmol) in ethanol (15 mL) was heated to reflux and monitored by TLC. After 15–30 min, the reaction was judged complete and on cooling, the mixture was filtered. The amorphous solid obtained was crystallized from a suitable solvent.

6.1.6.4. Method D. For some compounds, the product appeared sensitive to heat; in these cases, the reaction was accomplished by stirring the starting materials in ethanol at r.t. for 24 h, using the same proportions as in method C.

Recrystallization solvents and physical data of compounds **12a**–**j** and **18a**–**j** are given in Table 1. Their spectroscopic data are summarized as follows.

12a: see Section 3. Anal. $C_{24}H_{18}N_2O_6$ (C, H, N).

12b: IR (cm^{-1}) *v* 3300 (NH), 1760 (CO ester), 1650 (CO ketone), 1620 (C=N), 1520 δ (NH); ^{1}H NMR (δ) 2.36 and 2.40 [2(s, 3H, CO–C*H*$_3$)], 6.84 (t, 1H, *H4′*, $^3J = 7.3$ Hz), 7.08 (s, 1H, *H7*), 7.28 (t, 1H, *H5′*, $^3J = 7.4$ Hz), 7.36 (d, 1H, *H6′*, $^3J = 7.8$ Hz), 7.44 (s, 1H, *H5*), 7.48 (t, 1H, *H2*, $^3J = 7.5$ Hz), 7.64 (d, 1H, *H3′*, $^3J = 8.2$ Hz), 8.05 (d, 1H, *H1*, $^3J = 7.4$ Hz), 8.37 (d, 1H, *H3*, $^3J = 7.4$ Hz), 8.90 (s, 1H, *H10*), 10.24 (s, 1H, N*H*). Anal. $C_{24}H_{17}ClN_2O_6$ (C, H, N).

12c: IR (cm^{-1}) *v* 3300 (NH), 1770, 1740 (CO ester), 1650 (CO ketone), 1620 (C=N), 1530 δ (NH); ^{1}H NMR (δ) 2.35 and 2.39 [2(s, 3H, CO–C*H*$_3$)], 6.81 (d, 1H, *H4′*, $^3J = 7.7$ Hz), 7.04 (d, 1H, *H6′*, $^3J = 8.0$ Hz), 7.08 (s, 1H, *H7*), 7.19 (s, 1H, *H2′*), 7.25 (t, 1H, *H5′*, $^3J = 8.0$ Hz), 7.44 (s, 1H, *H5*), 7.49 (t, 1H, *H2*, $^3J = 7.7$ Hz), 8.04 (d, 1H, *H1*, $^3J = 7.9$ Hz), 8.36 (d, 1H, *H3*, $^3J = 7.5$ Hz), 8.50 (s, 1H, *H10*), 11.04 (s, 1H, N*H*); ^{13}C NMR (δ) 125.2 *C1*, 124.5 *C2*, 130.3 *C3*, 124.5 *C4*, 151.7 *C4a*, 156.6 *C4b*, 108.9 *C5*, 154.8 *C6*, 113.2 *C7*, 150.5 *C8*, 112.1 *C8a*, 173.9 *C9*, 121.8 *C9a*, 168.1 and 168.6 [2*C*=O (Ac)], 20.7 and 20.8 [2*C*H$_3$ (Ac)], 130.5 *C10*, 146.3 *C1′*, 111.5 *C2′*, 133.8 *C3′*, 118.7 *C4′*, 130.6 *C5′*, 110.9 *C6′*. Anal. $C_{24}H_{17}ClN_2O_6$ (C, H, N).

12d: IR (cm^{-1}) ν 3300 (NH), 1770, 1740 (CO ester), 1650 (CO ketone), 1620 (C=N), 1560, 1530 δ (NH); ^1H NMR (δ) 2.37 and 2.41 [2(s, 3H, CO–CH_3)], 7.11 (d, 1H, *H7*, $^4J = 2.2$ Hz), 7.16 (d, 2H, *H2′ + H6′*, $^3J = 8.8$ Hz), 7.30 (d, 2H, *H3′ + H5′*, $^3J = 8.8$ Hz), 7.47 (d, 1H, *H5*, $^4J = 2.2$ Hz), 7.50 (t, 1H, *H2*, $^3J = 7.8$ Hz), 8.06 (d, 1H, *H1*, $^3J = 6.5$ Hz), 8.38 (d, 1H, *H3*, $^3J = 6.5$ Hz), 8.48 (s, 1H, *H10*), 10.90 (s, 1H, N*H*). Anal. $C_{24}H_{17}ClN_2O_6$ (C, H, N).

12e: IR (cm^{-1}) ν 3300 (NH), 1770 (CO ester), 1660 (CO ketone), 1620 (C=N), 1560, 1520 δ (NH); ^1H NMR (δ) 2.36 and 2.40 [2(s, 3H, CO–CH_3)], 6.81 (d, 1H, *H6′*, $^3J = 5.2$ Hz), 7.07 (s, 1H, *H7*), 7.13 (t, 1H, *H4′*, $^3J = 7.3$ Hz), 7.17 (d, 1H, *H3′*, $^3J = 9.5$ Hz), 7.41 (s, 1H, *H5*), 7.47 (t, 1H, *H2*, $^3J = 7.5$ Hz), 7.59 (t, 1H, *H5′*, $^3J = 7.9$ Hz), 8.04 (d, 1H, *H1*, $^3J = 7.7$ Hz), 8.36 (d, 1H, *H3*, $^3J = 7.3$ Hz), 8.75 (s, 1H, *H10*), 10.60 (s, 1H, N*H*). Anal. $C_{24}H_{17}FN_2O_6$ (C, H, N).

12f: IR (cm^{-1}) ν 3300 (NH), 1770, 1740 (CO ester), 1660 (CO ketone), 1620 (C=N), 1560, 1540 δ (NH); ^1H NMR (δ) 2.36 and 2.40 [2(s, 3H, CO–CH_3)], 6.58 (t, 1H, *H5′*, $^3J = 8.3$ Hz), 6.90 (d, 1H, *H6′*, $^3J = 7.8$ Hz), 6.96 (d, 1H, *H2′*, ^3J [H–F] = 11.3 Hz), 7.10 (d, 1H, *H7*, $^4J = 2.2$ Hz), 7.27 (dd, 1H, *H4′*, $^3J = 7.4$ Hz, ^3J [H–F] = 14.4 Hz), ^3J [H–F] = 11.3 Hz), 7.46 (d, 1H, *H5*, $^4J = 2.2$ Hz), 7.49 (t, 1H, *H2*, $^3J = 7.6$ Hz), 8.06 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J = 1.7$ Hz), 8.40 (dd, 1H, *H3*, $^3J = 7.4$ Hz, $^4J = 1.7$ Hz), 8.49 (s, 1H, *H10*), 10.95 (s, 1H, N*H*). Anal. $C_{24}H_{17}FN_2O_6$ (C, H, N).

12g: IR (cm^{-1}) ν 3300 (NH), 1770, 1740 (CO ester), 1655 (CO ketone), 1620 (C=N), 1560, 1540 δ (NH); ^1H NMR (δ) 2.35 and 2.38 [2(s, 3H, CO–CH_3)], 7.05 (d, 1H, *H7*, $^4J = 2.2$ Hz), 7.07–7.14 (m, 4H, *H2′ + H3′ + H5′ + H6′*), 7.41 (d, 1H, *H5*, $^4J = 2.1$ Hz), 7.43 (t, 1H, *H2*, $^3J = 7.8$ Hz), 7.99 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J =$ 1.6 Hz), 8.31 (dd, 1H, *H3*, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz), 8.39 (s, 1H, *H10*), 10.70 (s, 1H, N*H*); ^{13}C NMR (δ) 124.6 *C1*, 124.3 *C2*, 129.7 *C3*, 124.8 *C4*, 151.4 *C4a*, 156.5 *C4b*, 108.8 *C5*, 154.8 *C6*, 113.1 *C 7*, 150.4 *C8*, 112.00 *C8a*, 173.8 *C9*, 121.7 *C9a*, 168.1 and 168.6 [2*C*=O (Ac)], 20.7 and 20.9 [2*C*H$_3$ (Ac)], 128.7 *C10*, 141.4 *C1′*, 113.2 *C2′*, 115.6 *C3′*, 156.1 *C4′*, 115.4 *C5′*, 113.1 *C6′*. Anal. $C_{24}H_{17}FN_2O_6$ (C, H, N).

12h: IR (cm^{-1}) ν 3300 (NH), 1760 (CO ester), 1650 (CO ketone), 1620 (C=N), 1570 δ (NH); ^1H NMR (δ) 2.36 and 2.40 [2(s, 3H, CO–CH_3)], 7.10 (d, 1H, *H7*, $^4J = 1.6$ Hz), 7.34 (dd, 1H, *H5′*, $^3J = 8.9$ Hz, $^4J = 1.8$ Hz), 7.46 (d, 1H, *H5*, $^4J = 1.6$ Hz), 7.50 (t, 1H, *H2*, $^3J = 7.5$ Hz), 7.52 (s, 1H, *H3′*), 7.65 (d, 1H, *H6′*, $^3J = 9.1$ Hz), 8.09 (d, 1H, *H1*, $^3J = 7.1$ Hz), 8.40 (d, 1H, *H3*, $^3J = 7.5$ Hz), 8.95 (s, 1H, *H10*), 10.41 (s, 1H, N*H*). Anal. $C_{24}H_{16}Cl_2N_2O_6$ (C, H, N).

12i: IR (cm^{-1}) ν 3300 (NH), 1770, 1750 (CO ester), 1650 (CO ketone), 1620 (C=N), 1580 δ (NH); ^1H NMR (δ) 2.37 and 2.41 [2(s, 3H, CO–CH_3)], 6.89 (d, 1H, *H4′*, $^3J = 8.5$ Hz), 7.12 (s, 1H, *H7*), 7.42 (d, 1H, *H3′*, $^3J = 8.5$ Hz), 7.47 (s, 1H, *H5*), 7.54 (t, 1H, *H2*, $^3J = 7.7$ Hz), 7.64 (s, 1H, *H6′*), 8.12 (d, 1H, *H1*, $^3J = 7.9$ Hz), 8.45 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.99 (s, 1H, *H10*), 10.49 (s, 1H, N*H*). Anal. $C_{24}H_{16}Cl_2N_2O_6$ (C, H, N).

12j: IR (cm^{-1}) ν 3300 (NH), 1770, 1740 (CO ester), 1660 (CO ketone), 1620 (C=N), 1560, 1530 δ (NH); ^1H NMR (δ) 2.36 and 2.40 [2(s, 3H, CO–CH_3)], 7.03 (t, 1H, *H3′*, ^3J [H–F] = 8.4 Hz), 7.09 (d, 1H, *H7*, $^4J = 1.1$ Hz), 7.24 (t, 1H, *H5′*, $^3J = 10.3$ Hz), 7.43 (d, 1H, *H5*, $^4J = 1.1$ Hz), 7.49 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.59 (dt, 1H, *H6′*, $^3J = 9.1$ Hz, ^4J [H–F] = 6.1 Hz), 8.06 (d, 1H, *H1*, $^3J = 7.6$ Hz), 8.38 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.75 (s, 1H, *H10*), 10.59 (s, 1H, N*H*). Anal. $C_{24}H_{16}F_2N_2O_6$ (C, H, N).

18a: IR (cm^{-1}) ν 3300 (NH), 1780 (CO ester), 1650 (CO ketone), 1570 δ (NH); ^1H NMR (δ) 2.49 and 2.50 [2(s, 3H, CO–CH_3)], 6.81 (t, 1H, *H4′*, $^3J = 7.2$ Hz), 7.16 (d, 2H, *H2′ + H6′*, $^3J = 7.8$ Hz), 7.26 (d, 2H, *H3′ + H5′*, $^3J = 7.8$ Hz), 7.50 (t, 1 H, *H2*, $^3J = 7.7$ Hz), 8.00 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J = 1.5$ Hz), 8.40 (dd, 1H, *H3*, $^3J = 7.7$ Hz, $^4J = 1.4$ Hz), 8.48 (s, 1H, *H10*), 10.87 (s, 1H, N*H*); ^{13}C NMR (δ) 124.5 *C1*, 125.1 *C2*, 130.1 *C3*, 125.4 *C4*, 151.1 *C4a*, 150.8 *C4b*, 115.2 *C5*, 148.1 *C6*, 117.9 *C7*, 145.0 *C8*, 113.9 *C8a*, 173.3 *C9*, 121.4 *C9a*, 166.5 and 167.5 [2*C*=*O* (Ac)], 19.8 and 20.3 [2*C*H$_3$ (Ac)], 127.9 *C10*, 144.6 *C1′*, 112.2 *C2′*, 129.0 *C3′*, 119.4 *C4′*, 129.0 *C5′*, 112.2 *C6′*. Anal. $C_{24}H_{16}Cl_2N_2O_6$ (C, H, Cl, N).

18b: IR (cm^{-1}) ν 3300 (NH), 1770 (CO ester), 1660 (CO ketone), 1560, 1520 δ (NH); ^1H NMR (δ) 2.49 and 2.53 [2(s, 3H, CO–CH_3)], 6.86 (td, 1H, *H4′*, $^3J = 7.5$ Hz, $^4J = 1.4$ Hz), 7.29 (t, 1H, *H5′*, $^3J = 7.6$ Hz), 7.37 (dd, 1H, *H6′*, $^3J = 8.0$ Hz, $^4J = 1.4$ Hz), 7.55 (t, 1H, *H2*, $^3J = 7.8$ Hz), 7.68 (d, 1H, *H3′*, $^3J = 8.2$ Hz), 8.08 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J = 1.4$ Hz), 8.49 (dd, 1H, *H3*, $^3J = 7.7$ Hz, $^4J = 1.4$ Hz), 8.89 (s, 1H, *H10*), 10.58 (s, 1H, N*H*). Anal. $C_{24}H_{15}Cl_3N_2O_6$ (C, H, Cl, N).

18c: IR (cm^{-1}) ν 3300 (NH), 1790, 1750 (CO ester), 1660 (CO ketone), 1560, 1520 δ (NH); ^1H NMR (δ) 2.49 and 2.55 [2(s, 3H, CO–CH_3)], 6.83 (d, 1H, *H4′*, $^3J = 8.$ 0 Hz), 7.05 (d, 1H, *H6′*, $^3J = 8.0$ Hz), 7.21 (d, 1H, *H2′*, $^4J = 1.7$ Hz), 7.27 (t, 1H, *H5′*, $^3J = 8.0$ Hz), 7.55 (t, 1H, *H2*, $^3J = 7.6$ Hz), 8.06 (dd, 1H, *H1*, $^3J = 7.6$ Hz, $^4J = 1.7$ Hz), 8.46 (dd, 1H, *H3*, $^3J = 7.6$ Hz, $^4J =$ 1.7 Hz), 8.51 (s, 1H, *H10*), 11.06 (s, 1H, NH); ^{13}C NMR (δ) 125.2 *C1*, 126.0 *C2*, 131.4 *C3*, 126.0 *C4*, 152.5 *C4a*, 158.3 *C4b*, 119.6 *C5*, 147.6 *C6*, 122.6 *C7*, 147.4 *C8*, 115.0 *C8a*, 173.5 *C9*, 122.7 *C9a*, 167.4 and 168.6 [2*C*=*O* (Ac)], 20.8 [2 *C*H$_3$ (Ac)], 130.3 *C10*, 146.5 *C1′*, 112.6 *C2′*, 135.1 *C3′*, 119.8 *C4′*, 131.2 *C5′*, 111.8 *C6′*. Anal. $C_{24}H_{15}Cl_3N_2O_6$ (C, H, Cl, N).

18d: IR (cm^{-1}) ν 3300 (NH), 1790, 1750 (CO ester), 1660 (CO ketone), 1560, 1530 δ (NH); ^1H NMR (δ) 2.49 and 2.54 [2(s, 3H, CO–CH_3)], 7.16 (dd, 2H, *H2′ +*

H6′, $^3J = 9.1$ Hz, $^4J = 2.2$ Hz), 7.29 (dd, 2H, *H3′* + *H5′*, $^3J = 8.7$ Hz, $^4J = 1.8$ Hz), 7.54 (t, 1H, *H2*, $3J = 7.8$ Hz), 8.05 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz), 8.43 (dd, 1H, *H3*, $^3J = 7.6$ Hz, $^4J = 1.8$ Hz), 8.49 (s, 1H, *H10*), 11.01 (s, 1H, N*H*). Anal. $C_{24}H_{15}Cl_3N_2O_6$ (C, H, Cl, N).

18e: IR (cm^{-1}) *v* 3300 (NH), 1790, 1760 (CO ester), 1660 (CO ketone), 1620 (C=N), 1560, 1530 *δ* (NH); ^{1}H NMR (*δ*) 2.49 and 2.55 [2(s, 3H, CO–C*H*$_3$)], 6.83 (m, 1H, *H6′*), 7.14 (t, 1H, *H4′*, $^3J = 7.8$ Hz), 7.18 (ddd, 1H, *H3′*, ^3J [H–F] = 12.2 Hz, $^3J = 8.2$ Hz, $^4J = 1.1$ Hz), 7.54 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.62 (td, 1H, *H5′*, $^3J = 8.2$ Hz, $^4J = 1.4$ Hz), 8.06 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz), 8.47 (dd, 1H, *H3*, $^3J = 7.6$ Hz, $^4J = 1.4$ Hz), 8.48 (s, 1H, *H10*), 10.90 (s, 1H, N*H*). Anal. $C_{24}H_{15}Cl_2FN_2O_6$ (C, H, Cl, N).

18f: IR (cm^{-1}) *v* 3300 (NH), 1780 (CO ester), 1660 (CO ketone), 1610 (C=N), 1570 *δ* (NH); ^{1}H NMR (*δ*) 2.49 and 2.55 [2(s, 3H, CO–C*H*$_3$)], 6.60 (t, 1H, *H5′*, $^3J = 8.3$ Hz), 6.91 (d, 1H, *H6′*, $^3J = 8.3$ Hz), 6.98 (d, 1H, *H2′*, ^3J [H–F] = 11.5 Hz), 7.27 (dd, 1H, *H4′*, ^3J [H–F] = 15.1 Hz, $^3J = 7.9$ Hz), 7.54 (t, 1H, *H2*, $^3J = 7.7$ Hz), 8.06 (d, 1H, *H1*, $^3J = 7.9$ Hz), 8.47 (d, 1H, *H3*, $^3J = 7.5$ Hz), 8.51 (s, 1H, *H10*), 11.08 (s, 1H, N*H*). Anal. $C_{24}H_{15}Cl_2FN_2O_6$ (C, H, Cl, N).

18g: IR (cm^{-1}) *v* 3300 (NH), 1790, 1750 (CO ester), 1660 (CO ketone), 1560, 1530 *δ* (NH); ^{1}H NMR (*δ*) 2.47 and 2.50 [2(s, 3H, CO–C*H*$_3$)], 7.07–7.12 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.47 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.98 (d, 1H, *H1*, $^3J = 7.5$ Hz), 8.35 (d, 1H, *H3*, $^3J = 7.3$ Hz), 8.38 (s, 1H, *H10*), 10.83 (s, 1H, N*H*); ^{13}C NMR (*δ*) 125.0 *C1*, 124.5 *C2*, 130.0 *C3*, 125.3 *C4*, 155.2 *C4a*, 157.1 *C4b*, 115.1 *C5*, 151.0 *C6*, 117.9 *C7*, 150.7 *C8*, 113.8 *C8a*, 173.2 *C9*, 121.3 *C9a*, 166.4 and 167.5 [2*C*=O (Ac)], 19.8 and 20.3 [2*C*H$_3$ (Ac)], 127.8 *C10*, 141.3 *C1′*, 113.2 *C2′*, 115.6 *C3′*, 146.5 *C4′*, 115.4 *C5′*, 113.2 *C6′*. Anal. $C_{24}H_{15}Cl_2FN_2O_6$ (C, H, Cl, N).

18h: IR (cm^{-1}) *v* 3300 (NH), 1780 (CO ester), 1660 (CO ketone), 1560, 1520 *δ* (NH); ^{1}H NMR (*δ*) 2.51 and 2.56 [2(s, 3H, CO–C*H*$_3$)], 7.36 (m, 1H, *H5′*), 7.53 (s, 1H, *H3′*), 7.57 (t, 1H, *H2*, $^3J = 6.0$ Hz), 7.69 (d, 1H, *H6′*, $^3J = 6.5$ Hz), 8.12 (d, 1H, *H1*, $^3J = 5.5$ Hz), 8.51 (d, 1H, *H3*, $^3J = 5.5$ Hz), 8.93 (s, 1H, *H10*), 10.72 (s, 1H, N*H*). Anal. $C_{24}H_{14}Cl_4N_2O_6$ (C, H, Cl, N).

18i: IR (cm^{-1}) *v* 3300 (NH), 1770 (CO ester), 1660 (CO ketone), 1570 *δ* (NH); ^{1}H NMR (*δ*) 2.50 [2(s, 3H, CO–C*H*$_3$)], 6.89 (dd, 1H, *H4′*, $^3J = 8.4$ Hz, $^4J = 2.4$ Hz), 7.40 (d, 1H, *H3′*, $^3J = 8.4$ Hz), 7.58 (t, 1H, *H2*, $^3J = 7.7$ Hz), 7.64 (d, 1H, *H6′*, $^4J = 2.5$ Hz), 8.11 (dd, 1H, *H1*, $^3J = 7.7$ Hz, $^4J = 1.4$ Hz), 8.52 (dd, 1H, *H3*, $^3J = 7.4$ Hz, $^4J = 1.4$ Hz), 8.94 (s, 1H, *H10*), 10.75 (s, 1H, N*H*). Anal. $C_{24}H_{14}Cl_4N_2O_6$ (C, H, Cl, N).

18j: IR (cm^{-1}) *v* 3300 (NH), 1790, 1760 (CO ester), 1660 (CO ketone), 1570, 1530 *δ* (NH); ^{1}H NMR (*δ*) 2.48 and 2.55 [2(s, 3H, CO–C*H*$_3$)], 7.03 (t, 1H, *H3′*, ^3J [H–F] = 8.8 Hz), 7.25 (d, 1H, *H5′*, $^3J = 10.2$ Hz), 7.54 (t, 1H, *H2*, $^3J = 7.4$ Hz), 7.61 (dt, 1H, *H6′*, $^3J = 8.8$ Hz, ^4J [H–F] = 6.4 Hz), 8.07 (d, 1H, *H1*, $^3J = 7.4$ Hz), 8.46 (d, 1H, *H3*, $^3J = 8.3$ Hz), 8.76 (s, 1H, *H10*), 10.86 (s, 1H, N*H*). Anal. $C_{24}H_{14}Cl_2F_2N_2O_6$ (C, H, Cl, N).

*6.1.7. 6,8-Dihydroxy-9-oxo-9H-xanthene-4-carboxaldehyde arylhydrazones (**13**, **19**)*

6.1.7.1. Method E. In a typical procedure, to a suspension of diacetoxyxanthone **12** (0.3 mmol) in 20 mL of mixture 1-propanol–water (1:1) was added sodium hydrogencarbonate (3 mmol), under vigorous stirring. The reaction mixture was then heated under reflux until TLC indicated no starting diacetate remained (1.5–12 h). Evaporation of the solvent gave a residue which was suspended in water and extracted with ethyl acetate (3×15 mL). The organic layer was washed with water, dried on sodium sulphate and evaporated to afford a gummy residue which was triturated with hexane or heptane until solid. The product was collected by vacuum filtration, dried and recrystallized.

6.1.7.2. Method F. A suspension of the appropriate diacetate **12** (0.5 mmol) in ethanol (5 mL) was treated with 10% aqueous sodium hydroxide solution (5 mL) and the reaction mixture was warmed at 55 °C for 30 min, under vigorous stirring. After cooling and neutralization with 1 N hydrochloric acid, the solid precipitate was collected by filtration, washed with water and dried to afford the expected diphenol, which was recrystallized from an appropriate solvent. Recrystallization solvents and physical data of compounds **13**–**19** are given in Table 2 while their spectroscopic data are summarized as follows.

13a: IR (cm^{-1}) *v* 3200 (OH), 3300 (NH), 1650 (CO), 1620 (C=N), 1580, 1560 *δ* (NH); ^{1}H NMR (*δ*) 6.21 (d, 1H, *H7*, $^4J = 1.9$ Hz), 6.36 (d, 1H, *H5*, $^4J = 1.9$ Hz), 6.79 (t, 1H, *H4′*, $^3J = 7.2$ Hz), 7.13 (d, 2H, *H2′* + *H6′*, $^3J = 7.9$ Hz), 7.24 (t, 2H, *H3′* + *H5′*, $^3J = 7.7$ Hz), 7.43 (t, 1H, *H2*, $^3J = 7.7$ Hz), 7.99 (d, 1H, *H1*, $^3J = 7.7$ Hz), 8.30 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.38 (s, 1H, *H10*), 10.73 (s, 1H, O*H*-6), 11.13 (br, 1H, N*H*), 12.77 (s, 1H, O*H*-8); ^{13}C NMR (*δ*) 123.9 *C1*, 124.0 *C2*, 129.8 *C3*, 124.7 *C4*, 151.9 *C4a*, 156.9 *C4b*, 93.9 *C5*, 165.9 *C6*, 98.2 *C7*, 162.8 *C8*, 102.0 *C8a*, 179.5 *C9*, 120.2 *C9a*, 128.7 *C10*, 144.8 *C1′*, 112.2 *C2′*, 129.0 *C3′*, 119.2 *C4′*, 129.0 *C5′*, 112.2 *C6′*. Anal. $C_{20}H_{14}N_2O_4$ (C, H, N).

13b: IR (cm^{-1}) *v* 3200 (OH), 3300 (NH), 1650 (CO), 1560 *δ* (NH); ^{1}H NMR (*δ*) 5.80 (s, 1H, *H7*), 6.02 (s, 1H, *H5*), 6.82 (t, 1H, *H4′*, $^3J = 7.4$ Hz), 7.28 (t, 1H, *H5′*, $^3J = 7.4$ Hz), 7.35 (d, 1H, *H6′*, $^3J = 8.1$ Hz), 7.38 (t, 1H, *H2*, $^3J = 8.1$ Hz), 7.64 (d, 1H, *H3′*,

$^3J = 8.1$ Hz), 7.99 (d, 1H, *H1*, $^3J = 7.6$ Hz), 8.26 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.87 (s, 1H, *H10*), 10.31 (br s, 2H, N*H* and O*H*-6), 12.89 (s, 1H, O*H*-8). Anal. $C_{20}H_{13}ClN_2O_4$ (C, H, N).

13c: IR (cm^{-1}) *v* 3400 (OH), 3300 (N–H), 1650 (CO), 1560, 1520 δ (NH); ^{1}H NMR (δ) 6.08 (d, 1H, *H7*, $^4J = 1.9$ Hz), 6.27 (d, 1H, *H5*, $^4J = 1.8$ Hz), 6.79 (dt, 1H, *H4′*, $^3J = 7.8$ Hz, $^4J = 1.2$ Hz), 7.01 (dd, 1H, *H6′*, $^3J = 8.2$ Hz, $^4J = 1.2$ Hz), 7.16 (t, 1H, *H2′*, $^4J = 2.0$ Hz), 7.24 (t, 1H, *H5′*, $^3J = 8.0$ Hz), 7.43 (t, 1H, *H2*, $^3J = 7.7$ Hz), 8.03 (dd, 1H, *H1*, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz), 8.31 (dd, 1H, *H3*, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz), 8.44 (s, 1H, *H10*), 10.91 (br s, 2H, N*H* and O*H*-6), 12.80 (s, 1H, O*H*-8); ^{13}C NMR (δ) 124.4 *C1*, 123.6 *C2*, 129.6 *C3*, 124.0 *C4*, 152.0 *C4a*, 157.1 *C4b*, 94.6 *C5*, 170.0 *C6*, 99.2 *C7*, 162.7 *C8*, 100.6 *C8a*, 178.2 *C9*, 120.4 *C9a*, 130.3 *C10*, 146.3 *C1′*, 111.3 *C2′*, 133.8 *C3′*, 118.5 *C4′*,130.5 *C5′*, 110.8 *C6′*. Anal. $C_{20}H_{13}ClN_2O_4$ (C, H, N).

13d: IR (cm^{-1}) *v* 3200 (OH), 3300 (NH), 1650 (CO), 1560, 1520 δ (NH); ^{1}H NMR (δ) 6.22 (s, 1H, *H7*), 6.38 (s, 1H, *H5*), 7.13 (d, 2H, *H2′* + *H6′*, $^3J = 8.0$ Hz), 7.28 (d, 2H, *H3′* + *H5′*, $^3J = 7.5$ Hz), 7.45 (t, 1H, *H2*, $^3J =$ 7.8 Hz), 8.03 (d, 1H, *H1*, $^3J = 8.0$ Hz), 8.32 (d, 1H, *H3*, $^3J = 7.5$ Hz), 8.40 (s, 1H, *H10*), 10.86 (s, 1H, O*H*-6), 11.18 (br, 1H, N*H*), 12.77 (s, 1H, O*H*-8). Anal. $C_{20}H_{13}ClN_2O_4$ (C, H, N).

13e: IR (cm^{-1}) *v* 3500 (OH), 3300 (N–H), 1650 (CO), 1620 (C=N), 1570, 1530 δ (NH); ^{1}H NMR (δ) 6.23 (d, 1H, *H7*, $^4J = 1.6$ Hz), 6.39 (d, 1H, *H5*, $^4J = 1.6$ Hz), 6.82 (dd, 1H, *H6′*, $^3J = 12.0$ Hz, ^3J [H–F] = 6.5 Hz), 7.14 (t, 1H, *H4′*, $^3J = 7.6$ Hz), 7.18 (dd, 1H, *H3′*, $^3J = 7.6$ Hz, ^3J [H–F] = 11.4 Hz), 7.49 (t, 1H, *H2*, $^3J = 7.9$ Hz), 7.60 (t, 1H, *H5′*, $^3J = 8.2$ Hz), 8.07 (dd, 1H, *H1*, $^3J = 7.6$ Hz, $^4J = 1.6$ Hz), 8.37 (dd, 1H, *H3*, $^3J = 7.9$ Hz, $^4J = 1.4$ Hz), 8.75 (s, 1H, *H10*), 10.65 (s, 1H, O*H*-6), 11.25 (br, 1H, N*H*), 12.77 (s, 1H, O*H*-8). Anal. $C_{20}H_{13}FN_2O_4$ (C, H, N).

13f: IR (cm^{-1}) *v* 3200 (OH), 3300 (NH), 1650 (C=O), 1560 δ (NH); ^{1}H NMR (δ) 6.25 (s, 1H, *H7*), 6.41 (s, 1H, *H5*), 6.59 (t, 1H, *H5′*, $^3J = 8.5$ Hz), 6.90 (d, 1H, *H6′*, $^3J = 8.3$ Hz), 6.91 (d, 1H, *H2′*, ^3J [H–F] = 11.1 Hz), 7.27 (dd, 1H, *H4′*, $^3J = 7.9$ Hz, ^3J [H–F] = 15.0 Hz), 7.50 (t, 1H, *H2*, $^3J = 7.6$ Hz), 8.08 (d, 1H, *H1*, $^3J = 7.8$ Hz), 8.39 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.47 (s, 1H, *H10*), 10.96 (s, 1H, O*H*-6), 11.22 (br, 1H, N*H*), 12.80 (s, 1H, O*H*-8). Anal. $C_{20}H_{13}FN_2O_4$ (C, H, N).

13g: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1580, 1560 δ (N–H); ^{1}H NMR (δ) 6.23 (s, 1H, *H7*), 6.39 (d, 1H, *H5*), 7.09–7.11 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.45 (t, 1H, *H2*, $^3J = 7.5$ Hz), 8.02 (d, 1H, *H1*, $^3J = 7.3$ Hz), 8.32 (d, 1H, *H3*, $^3J = 6.5$ Hz), 8.39 (s, 1H, *H10*), 10.75 (s, 1H, O*H*-6), 10.33 (br, 1H, N*H*), 12.78 (s, 1H, O*H*-8); ^{13}C NMR (δ) 124.0 *C1*, 124.1 *C2*, 129.9 *C3*, 124.7 *C4*, 151.9 *C4a*, 157.0 *C4b*, 93.9 *C5*, 166.0 *C6*, 98.3 *C7*, 162.8 *C8*, 101.9 *C8a*, 179.5 *C9*, 120.2 *C9a*, 128.8 *C10*, 141.4 *C1′*, 113.2 *C2′*, 115.7 *C3′*, 156.1 *C4′*, 115.5 *C5′*, 113.1 *C6′*. Anal. $C_{20}H_{13}FN_2O_4$ (C, H, N).

13h: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1570 δ (N–H); ^{1}H NMR (δ) 5.83 (s, 1H, *H7*), 6.04 (s, 1H, *H5*), 7.33 (d, 1H, *H5′*, $^3J = 5.4$ Hz), 7.39 (d, 1H, *H6′*, $^3J = 5.4$ Hz), 7.48 (s, 1H, *H3′*), 7.63 (t, 1H, *H2*, $^3J = 6.5$ Hz), 8.01 (d, 1H, *H1*, $^3J = 6.0$ Hz), 8.27 (d, 1H, *H3*, $^3J = 6.0$ Hz), 8.88 (s, 1H, *H10*), 10.43 (br s, 2H, N*H* and O*H*-6), 12.86 (s, 1H, O*H*-8). Anal. $C_{20}H_{12}Cl_2N_2O_4$ (C, H, N).

13i: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1570 δ (NH); ^{1}H NMR (δ) 5.53 (s, 1H, *H7*), 5.75 (s, 1H, *H5*), 6.84 (d, 1H, *H4′*, $^3J = 8.9$ Hz), 7.34 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.37 (d, 1H, *H3′*, $^3J = 7.6$ Hz), 7.58 (s, 1H, *H6′*), 7.95 (d, 1H, *H1*, $^3J = 6.4$ Hz), 8.22 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.89 (s, 1H, *H10*), 10.46 (br s, 2H, N*H* and O*H*-6), 12.92 (s, 1H, O*H*-8). Anal. $C_{20}H_{12}Cl_2N_2O_4$ (C, H, N).

13j: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1620 (C=N), 1570, 1530 δ (NH); ^{1}H NMR (δ) 5.99 (s, 1H, *H7*), 6.16 (s, 1H, *H5*), 7.02 (t, 1H, *H3′*, $^3J = 8.1$ Hz), 7.22 (td, 1H, *H5′*, $^3J = 9.1$ Hz, $^4J = 2.5$ Hz), 7.42 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.57 (dt, 1H, *H6′*, $^3J = 9.1$ Hz, ^4J [H–F] = 6.4 Hz), 8.02 (d, 1H, *H1*, $^3J = 7.6$ Hz), 8.29 (d, 1H, *H3*, $^3J = 7.6$ Hz), 8.70 (s, 1H, *H10*), 10.58 (s, 1H, O*H*-6), 10.34 (br, 1H, N*H*), 12.83 (s, 1H, O*H*-8). Anal. $C_{20}H_{12}F_2N_2O_4$ (C, H, N).

19a: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1620 (C=N), 1570 δ (NH); ^{1}H NMR (δ) 6.78 (t, 1H, *H4′*, $^3J = 6.3$ Hz), 7.14 (d, 2H, *H2′* + *H6′*, $^3J = 7.9$ Hz), 7.24 (t, 2H, *H3′* + *H5′*, $^3J = 7.1$ Hz), 7.37 (t, 1H, *H2*, $^3J = 7.1$ Hz), 7.92 (d, 1H, *H1*, $^3J = 7.9$ Hz), 8.24 (d, 1H, *H3*, $^3J = 6.3$ Hz), 8.45 (s, 1H, *H10*), 10.66 (s, 1H, O*H*-6), 10.79 (s, 1H, N*H*), 13.81 (s, 1H, O*H*-8). Anal. $C_{20}H_{12}Cl_2N_2O_4$ (C, H, N).

19b: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1570 δ (NH); ^{1}H NMR (δ) 6.84 (s, 1H, *H4′*), 7.28 (s, 1H, *H5′*), 7.36 (s, 1H, *H6′*), 7.38 (s, 1H, *H2*), 7.66 (d, 1H, *H3′*, $^3J = 6.6$ Hz), 7.98 (s, 1H, *H1*), 8.28 (s, 1H, *H3*), 8.83 (s, 1H, *H10*), 10.50 (br s, 2H, N*H* and O*H*-6), 13.83 (s, 1H, O*H*-8). Anal. $C_{20}H_{11}Cl_3N_2O_4$ (C, H, N).

19c: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1560 δ (NH); ^{1}H NMR (δ) 6.81 (s, 1H, *H4′*), 7.05 (s, 1H, *H6′*), 7.19 (s, 1H, *H2′*), 7.25 (s, 1H, *H5′*), 7.44 (s, 1H, *H2*), 7.99 (s, 1H, *H1*), 8.32 (s, 1H, *H3*), 8.47 (s, 1H, *H10*), 10.99 (br s, 1H, N*H* and O*H*-6), 13.64 (s, 1H, O*H*-8). Anal. $C_{20}H_{11}Cl_3N_2O_4$ (C, H, N).

19d: IR (cm^{-1}) *v* 3500 and 3400 (OH), 3300 (NH), 1650 (CO), 1560 δ (NH); ^{1}H NMR (δ) 7.15 (d, 2H, *H2′* + *H6′*, $^3J = 8.8$ Hz), 7.27 (d, 2H, *H3′* + *H5′*, $^3J =$ 8.3 Hz), 7.37 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.94 (d, 1H, *H1*, $^3J = 6.9$ Hz), 8.24 (d, 1H, *H3*, $^3J = 6.9$ Hz), 8.46 (s, 1H,

H10), 10.90 (br s, 2H, N*H* and O*H*-6), 13.79 (s, 1H, O*H*-8). Anal. $C_{20}H_{11}Cl_3N_2O_4$ (C, H, N).

19f: IR (cm^{-1}) ν 3400 (OH), 3300 (NH), 1640 (CO), 1560 δ (NH); ^{1}H NMR (δ) 6.56 (t, 1H, *H5′*, $^3J = 8.3$ Hz), 6.91 (d, 1H, *H6′*, $^3J = 8.3$ Hz), 6.95 (d, 1H, *H2′*, ^3J [H–F] = 11.6 Hz), 7.25 (dd, 1H, *H4′*, ^3J [H–F] = 14.8 Hz, $^3J = 7.9$ Hz), 7.36 (t, 1H, *H2*, $^3J = 7.6$ Hz), 7.95 (d, 1H, *H1*, $^3J = 7.4$ Hz), 8.27 (d, 1H, *H3*, $^3J =$ 7.9 Hz), 8.48 (s, 1H, *H10*), 10.97 (br s, 2H, N*H* and O*H*-6), 13.79 (s, 1H, O*H*-8). Anal. $C_{20}H_{11}Cl_2FN_2O_4$ (C, H, N).

19g: IR (cm^{-1}) ν 3450 (OH), 3300 (NH), 1650 (CO ketone), 1560, 1530 δ (NH); ^{1}H NMR (δ) 7.07–7.14 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.37 (t, 1H, *H2*, $^3J = 7.4$ Hz), 7.93 (d, 1H, *H1*, $^3J = 7.5$ Hz), 8.24 (d, 1H, *H3*, $^3J = 7.4$ Hz), 8.44 (s, 1H, *H10*), 10.80 (br s, 2H, N*H* and O*H*-6), 13.80 (s, 1H, O*H*-8); ^{13}C NMR (δ) 123.7 *C1*, 123.4 *C2*, 128.0 *C3*, 124.3 *C4*, 150.7 *C4a*, 151.0 *C4b*, 95.8 *C5*, 156.1 *C6*, 105.4 *C7*, 167.9 *C8*, 100.5 *C8a*, 174.5 *C9*, 120.4 *C9a*, 129.0 *C10*, 141.7 *C1′*, 113.2 *C2′*, 115.6 *C3′*, 156.2 *C4′*, 115.5 *C5′*, 113.2 *C6′*. Anal. $C_{20}H_{11}Cl_2FN_2O_4$ (C, H, N).

19h: IR (cm^{-1}) ν 3400 (OH), 1650 (CO), 1560 δ (NH); ^{1}H NMR (δ) 7.33 (dd, 1H, *H5′*, $^3J = 8.7$ Hz, $^4J = 2.1$ Hz), 7.39 (t, 1H, *H2*, $^3J = 7.7$ Hz), 7.48 (d, 1H, *H3′*, $^4J = 2.3$ Hz), 7.65 (d, 1H, *H6′*, $^3J = 8.9$ Hz), 7.99 (d, 1H, *H1*, $^3J = 7.5$ Hz), 8.28 (d, 1H, *H3*, $^3J =$ 7.5 Hz), 8.86 (s, 1H, *H10*), 10.63 (br s, 2H, N*H* and O*H*-6), 13.82 (s, 1H, O*H*-8). Anal. $C_{20}H_{10}Cl_4N_2O_4$ (C, H, N).

19i: IR (cm^{-1}) ν 3400 (OH), 3300 (NH), 1650 (CO), 1560 δ (NH); ^{1}H NMR (δ) 6.87 (d, 1H, *H4′*, $^3J = 8.3$ Hz), 7.40 (t, 1H, *H2*, $^3J = 9.2$ Hz), 7.42 (d, 1H, *H3′*, $^3J = 8.3$ Hz), 7.61 (d, 1H, *H6′*, $^4J = 2.8$ Hz), 8.00 (d, 1H, *H1*, $^3J = 8.3$ Hz), 8.31 (d, 1H, *H3*, $^3J = 7.4$ Hz), 8.89 (s, 1H, *H10*), 10.69 (br s, 2H, N*H* and O*H*-6), 13.81 (s, 1H, O*H*-8). Anal. $C_{20}H_{10}Cl_4N_2O_4$ (C, H, N).

19j: IR (cm^{-1}) ν 3600 and 3450 (OH), 3300 (NH), 1650 (CO), 1570, 1540 δ (NH); ^{1}H NMR (δ) 7.01 (t, 1H, *H3′*, ^3J [H–F] = 8.3 Hz), 7.22 (td, 1H, *H5′*, $^3J =$ 8.8 Hz, $^4J = 2.8$ Hz), 7.37 (t, 1H, *H2*, $^3J = 7.9$ Hz), 7.58 (dt, 1H, *H6′*, $^3J = 9.2$ Hz, ^4J [H–F] = 5.5 Hz), 7.95 (d, 1H, *H1*, $^3J = 7.4$ Hz), 8.26 (d, 1H, *H3*, $^3J =$ 8.3 Hz), 8.71 (s, 1H, *H10*), 10.77 (br s, 2H, N*H* and O*H*-6), 13.80 (s, 1H, O*H*-8). Anal. $C_{20}H_{10}Cl_2F_2N_2O_4$ (C, H, N).

6.1.8. 6,8-Diacetoxy-9-oxo-9H-xanthene-3-carboxaldehyde arylhydrazones ***20*** *and 6,8-dihydroxy-9-oxo-9H-xanthene-3-carboxaldehyde arylhydrazones* ***21***

The synthesis of these compounds was carried out starting from the corresponding 9-oxo-9*H*-xanthene-3-carboxaldehyde (0.4 g, 1.2 mmol), obtained by a reaction sequence similar to that shown in Fig. 3, using phloroglucinol and 4-methylsalicylic acid. Subsequent condensation with a suitable substituted hydrazine (phenylhydrazine, 3-chlorophenylhydrazine or 4-fluorophenylhydrazine) afforded the hydrazones **20**, which by hydrolysis gave the free hydroxylated derivatives **21**. Physical data of these compounds are listed in Table 3. Their main spectral characteristics are given as follows.

20a: IR (cm^{-1}) ν 3300 (NH), 1760 and 1740 (CO ester), 1640 (CO ketone), 1620 (C=N), 1560, 1540 δ (NH); ^{1}H NMR (δ) 2.34 and 2.39 [2(s, 3H, CO–CH_3)], 6.83 (t, 1H, *H4′*, $^3J = 7.2$ Hz), 7.03 (d, 1H, *H7*, $^4J =$ 2.2 Hz), 7.16 (d, 2H, *H2′* + *H6′*, $^3J = 7.7$ Hz), 7.26 (t, 2H, *H3′* + *H5′*, $^3J = 7.8$ Hz), 7.41 (d, 1H, *H5*, $^4J = 2.1$ Hz), 7.72 (s, 1H, *H4*), 7.76 (dd, 1H, *H2*, $^3J = 8.4$ Hz, $^4J = 1.0$ Hz), 7.94 (s, 1H, *H10*), 8.07 (d, 1H, *H1*, $^3J = 8.3$ Hz), 10.77 (s, 1H, N*H*); ^{13}C NMR (δ) 126.1 *C1*, 121.3 *C2*, 143.0 *C3*, 113.6 *C4*, 155.2 *C4a*, 157.0 *C4b*, 109.0 *C5*, 154.7 *C6*, 113.2 *C7*, 150.3 *C8*, 112.4 *C8a*, 173.4 *C9*, 120.1 *C9a*, 168.1 and 168.7 [2*C*=O (Ac)], 20.8 [2CH_3 (Ac)], 133.7 *C10*, 144.4 *C1′*, 112.5 *C2′*, 129.1 *C3′*, 119.7 *C4′*, 129.1 *C5′*, 112.6 *C6′*. Anal. $C_{24}H_{18}N_2O_6$ (C, H, N).

20c: IR (cm^{-1}) ν 3300 (NH), 1760 (CO ester), 1650 (CO ketone), 1620 ν(C=N), 1570, 1525 δ (NH); ^{1}H NMR (δ) 2.32 and 2.37 [2(s, 3H, CO–CH_3)], 6.80 (d, 1H, *H4′*, $^3J = 7.7$ Hz), 7.00 (d, 1H, *H7*, $^4J = 1.2$ Hz), 7.06 (d, 1H, *H6′*, $^3J = 8.0$ Hz), 7.19 (s, 1H, *H2′*), 7.23 (t, 1H, *H5′*, $^3J = 8.0$ Hz), 7.37 (d, 1H, *H5*, $^4J = 1.2$ Hz), 7.67 (s, 1H, *H4*), 7.72 (d, 1H, *H2*, $^3J = 8.3$ Hz), 7.97 (s, 1H, *H10*), 8.02 (d, 1H, *H1*, $^3J = 8.3$ Hz), 11.25 (s, 1H, N*H*); ^{13}C NMR (δ) 126.0 *C1*, 121.4 *C2*, 142.5 *C3*, 113.9 *C4*, 155.1 *C4a*, 157.0 *C4b*, 108.9 *C5*, 154.6 *C6*, 113.0 *C7*, 150.3 *C8*, 112.3 *C8a*, 173.4 *C9*, 120.3 *C9a*, 168.0 and 168.6 [2*C*=O (Ac)], 20.7 [2CH_3 (Ac)], 135.2 *C10*, 146.0 *C1′*, 111.7 *C2′*, 133.7 *C3′*,, 118.9 *C4′*, 130.5 *C5′*, 111.1 *C6′*. Anal. $C_{24}H_{17}ClN_2O_6$ (C, H, N).

20g: IR (cm^{-1}) ν 3300 (NH), 1760 (CO ester), 1650 (CO ketone), 1620 (C=N), 1540 δ (NH); ^{1}H NMR (δ) 2.32 and 2.38 [2(s, 3H, CO–CH_3)], 7.01 (d, 1H, *H7*, $^4J = 2.2$ Hz), 7.07–7.14 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.36 (d, 1H, *H5*, $^4J = 2.2$ Hz), 7.65 (d, 1H, *H4*, $^4J = 1.2$ Hz), 7.71 (dd, 1H, *H2*, $^3J = 8.4$ Hz, $^4J = 1.3$ Hz), 7.87 (s, 1H, *H10*), 8.02 (d, 1H, *H1*, $^3J = 8.3$ Hz), 10.77 (s, 1H, N*H*); ^{13}C NMR (δ) 126.0 *C1*, 121.3 *C2*, 142.9 *C3*, 113.5 *C4*, 155.1 *C4a*, 157.0 *C4b*, 108.9 *C5*, 154.6 *C6*, 113.0 *C7*, 150.3 *C8*, 112.3 *C8a*, 173.3 *C9*, 120.0 *C9a*, 168.0 and 168.6 [2*C*=O (Ac)], 20.7 (2CH_3 Ac), 133.7 *C10*, 141.0 *C1′*, 113.5 (*C2′* + *C6′*), 115.6 *C3′*, 156.4 *C4′*, 115.4 *C5′*. Anal. $C_{24}H_{17}FN_2O_6$ (C, H, N).

21a: IR (cm^{-1}) ν 3300 (NH), 1650 (CO), 1560 δ (NH); ^{1}H NMR (δ) 6.19 (s, 1H, *H7*), 6.38 (s, 1H, *H5*), 6.83 (t, 1H, *H4′*, $^3J = 6.9$ Hz), 7.16 (d, 2H, *H2′* + *H6′*, $^3J = 7.5$ Hz), 7.26 (t, 2H, *H3′* + *H5′*, $^3J =$

7.5 Hz), 7.68 (s, 1H, *H4*), 7.73 (d, 1H, *H2*, $^3J = 8.0$ Hz), 7.93 (s, 1H, *H10*), 8.07 (d, 1H, *H1*, $^3J = 8.2$ Hz), 10.76 (s, 1H, O*H*-6), 10.94 (br, 1H, N*H*), 12.87 (s, 1H, O*H*-8); ^{13}C NMR (δ) 125.4 *C1*, 121.0 *C2*, 143.0 *C3*, 113.4 *C4*, 155.8 *C4a*, 157.3 *C4b*, 94.0 *C5*, 165.6 *C6*, 98.0 *C7*, 162.8 *C8*, 102.2 *C8a*, 179.1 *C9*, 118.5 *C9a*, 133.8 *C10*, 144.4 *C1′*, 112.5 (*C2′* + *C6′*), 129.1 (*C3′* + *C5′*), 119.7 *C4′*. Anal. $C_{20}H_{14}N_2O_4$ (C, H, N).

21c: IR (cm^{-1}) *v* 3400 (OH), 3200 (NH), 1650 (CO), 1620 *v*(C=N), 1560, 1540 δ (NH); ^{1}H NMR (δ) 6.20 (s, 1H, *H7*), 6.39 (d, 1H, *H5*), 6.87 (d, 1H, *H4′*, $^3J = 7.7$ Hz), 7.08 (d, 1H, *H6′*, $^3J = 7.8$ Hz), 7.21 (s, 1H, *H2′*), 7.28 (t, 1H, *H5′*, $^3J = 8.0$ Hz), 7.79 (s, 1H, *H4*), 7.81 (d, 1H, *H2*, $^3J = 8.6$ Hz), 7.99 (s, 1H, *H10*), 8.12 (d, 1H, *H1*, $^3J = 8.2$ Hz), 11.12 (br, 1H, N*H*), 10.99 (s, 1H, O*H*-6), 12.90 (s, 1H, O*H*-8); ^{13}C NMR (δ) 126.2 *C1*, 121.9 *C2*, 143.4 *C3*, 114.8 *C4*, 156.8 *C4a*, 158.7 *C4b*, 95.3 *C5*, 164.3 *C6*, 99.5 *C7*, 162.7 *C8*, 102.6 *C8a*, 179.7 *C9*, 120.3 *C9a*, 136.7 *C10*, 147.3 *C1′*, 112.0 *C2′*, 135.1 *C3′*, 120.0 *C4′*, 131.4 *C5′*, 112.8 *C6′*. Anal. $C_{20}H_{13}ClN_2O_4$ (C, H, N).

21g: IR (cm^{-1}) *v* 3300 (NH), 1650 (CO), 1620 (C=N), 1570, 1520 δ (NH); ^{1}H NMR (δ) 6.19 (d, 1H, *H7*, $^4J = 1.8$ Hz), 6.38 (d, 1H, *H5*, $^4J = 1.8$ Hz), 7.09–7.13 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.69 (s, 1H, *H4*), 7.73 (d, 1H, *H2*, $^3J = 8.5$ Hz), 7.91 (s, 1H, *H10*), 8.06 (d, 1H, *H1*, $^3J = 8.3$ Hz), 10.81 (s, 1H, O*H*-6), 11.04 (br, 1H, N*H*), 12.88 (s, 1H, O*H*-8); ^{13}C NMR (δ) 125.3 *C1*, 121.0 *C2*, 143.0 *C3*, 113.5 *C4*, 155.7 *C4a*, 157.3 *C4b*, 93.9 *C5*, 165.6 *C6*, 98.0 *C7*, 162.7 *C8*, 102.2 *C8a*, 179.1 *C9*, 118.5 *C9a*, 133.8 *C10*, 141.1 *C1′*, 113.5 *C2′*, 115.6 *C3′*, 152.1 *C4′*, 115.5 *C5′*,113.5 *C6′*. Anal. $C_{20}H_{13}FN_2O_4$ (C, H, N).

6.1.9. 6,8-Diacetoxy-9-oxo-9H-xanthene-2-carboxaldehyde arylhydrazones ***22*** *and 6,8-dihydroxy-9-oxo-9H-xanthene-2-carboxaldehyde arylhydrazones* ***23***

According to the same protocol above described compounds **22** and **23** carrying the hydrazone chain at position 2 on the xanthone nucleus were prepared from phloroglucinol and 5-methylsalicylic acid as starting material (Table 4).

22a: IR (cm^{-1}) *v* 3300 (NH), 1780, 1740 (CO ester), 1660 *v*(CO ketone), 1620 (C=N), 1520 δ (NH); ^{1}H NMR (δ) 2.33 and 2.40 [2(s, 3H, CO–CH_3)], 6.77 (t, 1H, *H4′*, $^3J = 6.8$ Hz), 7.06 (s, 1H, *H7*), 7.10 (d, 2H, *H2′* + *H6′*, $^3J = 7.7$ Hz), 7.26 (t, 2H, *H3′* + *H5′*, $^3J =$ 7.3 Hz), 7.43 (s, 1H, *H5*), 7.60 (d, 1H, *H4*, $^3J = 8.5$ Hz), 7.95 (s, 1H, *H10*), 8.17 (d, 1H, *H3*, $^3J = 8.7$ Hz), 8.20 (s, 1H, *H1*), 10.47 (s, 1H, N*H*); ^{13}C NMR (δ) 122.3 *C1*, 132.6 *C2*, 131.8 *C3*, 118.3 *C4*, 154.2 *C4a*, 156.8 *C4b*, 109.1 *C5*, 154.8 *C6*, 113.2 *C7*, 150.4 *C8*, 112.2 *C8a*, 173.8 *C9*, 121.4 *C9a*, 168.0 and 168.6 [2*C*=O (Ac)], 20.7 [2*C*H$_3$ (Ac)]; 134.5 *C10*, 145.0 *C1′*, 112.0 *C2′*, 128.9 *C3′*, 118.9 *C4′*, 128.9 *C5′*, 112.0 *C6′*. Anal. $C_{24}H_{18}N_2O_6$ (C, H, N).

22c: IR (cm^{-1}) *v* 3300 (NH), 1770 (CO ester), 1650 (CO ketone), 1620 (C=N), 1540 δ (NH); ^{1}H NMR (δ) 2.33 and 2.40 [2(s, 3H, CO–CH_3)], 6.77 (d, 1H, *H4′*, $^3J = 5.7$ Hz), 6.99 (d, 1H, *H6′*, $^3J = 6.3$ Hz), 7.06 (s, 1H, *H7*), 7.12 (s, 1H, *H2′*), 7.22 (t, 1H, *H5′*, $^3J = 7.9$ Hz), 7.43 (s, 1H, *H5*), 7.61 (d, 1H, *H4*, $^3J = 6.9$ Hz), 7.97 (s, 1H, *H10*), 8.20 (m, 2H, *H3* + *H1*), 10.68 (s, 1H, N*H*); ^{13}C NMR (δ) 122.9 *C1*, 132.1 *C2*, 131.9 *C3*, 118.2 *C4*, 154.4 *C4a*, 156.8 *C4b*, 109.0 *C5*, 154.7 *C6*, 113.2 *C7*, 150.3 *C8*, 112.1 *C8a*, 173.7 *C9*, 121.4 *C9a*, 168.0 and 168.5 [2*C*=O (Ac)], 20.7 [2*C*H$_3$ (Ac)], 136.1 *C10*, 146.4 *C1′*, 111.3 *C2′*, 133.7 *C3′*, 118.3 *C4′*, 130.5 *C5′*, 110.7 *C6′*. Anal. $C_{24}H_{17}ClN_2O_6$ (C, H, N).

22g: IR (cm^{-1}) *v* 3300 (NH), 1760 (CO ester), 1660 (CO ketone), 1630 (C=N), 1540 δ (NH); ^{1}H NMR (δ) 2.33 and 2.39 [2(s, 3H, CO–CH_3)], 7.06 (d, 1H, *H7*, $^4J = 2.1$ Hz), 7.08–7.12 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.44 (d, 1H, *H5*, $^4J = 2.2$ Hz), 7.61 (d, 1H, *H4*, $^3J = 8.7$ Hz), 8.00 (s, 1H, *H10*), 8.16 (dd, 1H, *H3*, $^3J = 8.7$ Hz, $^4J = 2.2$ Hz), 8.19 (d, 1H, *H1*, $^4J = 2.1$ Hz), 10.73 (s, 1H, N*H*); ^{13}C NMR (δ) 122.2 *C1*, 132.6 *C2*, 131.8 *C3*, 118.2 *C4*, 154.2 *C4a*, 156.8 *C4b*, 109.0 *C5*, 154.7 *C6*, 113.2 *C7*, 150.3 *C8*, 112.1 *C8a*, 173.9 *C9*, 121.4 *C9a*, 168.0 and 168.5 [2*C*=O (Ac)], 20.7 [2*C*H$_3$ (Ac)], 134.5 *C10*, 141.7 *C1′*, 113.0 *C2′*, 115.4 *C3′*, 155.0 *C4′*, 115.2 *C5′*, 113.0 *C6′*. Anal. $C_{24}H_{17}FN_2O_6$ (C, H, N).

23a: IR (cm^{-1}) *v* 3500 (OH), 3300 (NH), 1650 (CO), 1620 (C=N), 1560 δ (NH); ^{1}H NMR (δ) 6.22 (s, 1H, *H7*), 6.40 (s, 1H, *H5*), 6.77 (s, 1H, *H4′*), 7.10 (d, 2H, *H2′* + *H6′*, $^3J = 6.6$ Hz), 7.23 (d, 2H, *H3′* + *H5′*, $^3J =$ 6.2 Hz), 7.58 (d, 1H, *H4*, $^3J = 7.9$ Hz), 7.98 (s, 1H, *H10*), 8.17 (d, 1H, *H3*, $^3J = 8.3$ Hz), 8.22 (s, 1H, *H1*), 10.46 (br s, 2H, N*H* and O*H*-6), 12.81 (s, 1H, O*H*-8); ^{13}C NMR (δ) 121.6 *C1*, 132.2 *C2*, 131.8 *C3*, 118.1 *C4*, 154.8 *C4a*, 157.2 *C4b*, 94.0 *C5*, 165.9 *C6*, 98.1 *C7*, 162.7 *C8*, 102.1 *C8a*, 179.4 *C9*, 119.9 *C9a*, 134.5 *C10*, 145.0 *C1′*, 112.0 (*C2′* + *C6′*), 128.9 (*C3′* + *C5′*), 118.85 *C4′*. Anal. $C_{20}H_{14}N_2O_4$ (C, H, N).

23c: IR (cm^{-1}) *v* 3400 (OH), 3300 (NH), 1650 (CO), 1620 (C=N); ^{1}H NMR (δ) 6.15 (d, 1H, *H7*, $^4J = 1.9$ Hz), 6.33 (d, 1H, *H5*, $^4J = 2.0$ Hz), 6.80 (m, 1H, *H4′*), 7.02 (dd, 1H, *H6′*, $^3J = 8.1$ Hz, $^4J = 1.2$ Hz), 7.14 (t, 1H, *H2′*, $^4J = 2.15$ Hz), 7.25 (t, 1H, *H5′*, $^3J = 8.0$ Hz), 7.61 (d, 1H, *H4*, $^3J = 8.7$ Hz), 8.03 (s, 1H, *H10*), 8.22 (dd, 1H, *H3*, $^3J = 8.8$ Hz, $^4J = 2.1$ Hz), 8.26 (d, 1H, *H1*, $^4J = 2.1$ Hz), 10.67 (br s, 1H, N*H* and O*H*-6), 12.83 (s, 1H, O*H*-8); ^{13}C NMR (δ) 123.2 *C1*, 135.0 *C2*, 132.4 *C3*, 118.9 *C4*, 156.3 *C4a*, 158.6 *C4b*, 95.4 *C5*, 162.7 *C6*, 99.7 *C7*, 161.7 *C8*, 102.6 *C8a*, 179.5 *C9*, 121.2 *C9a*, 137.4 *C10*, 147.8 *C1′*, 112.3 *C2′*, 132.8 *C3′*, 119.2 *C4′*, 131.3 *C5′*, 111.6 *C6′*. Anal. $C_{20}H_{13}ClN_2O_4$ (C, H, N).

23g: IR (cm^{-1}) ν 3400 (OH), 3300 (NH), 1660 (CO); ^1H NMR (δ) 6.23 (s, 1H, *H7*), 6.41 (s, 1H, *H5*), 7.09–7.11 (m, 4H, *H2′* + *H3′* + *H5′* + *H6′*), 7.62 (d, 1H, *H4*, $^3J = 8.6$ Hz), 8.00 (s, 1H, *H10*), 8.20 (d, 1H, *H3*, $^3J = 8.5$ Hz), 8.26 (s, 1H, *H1*), 10.48 (s, 1H, O*H*-6), 11.17 (s, 1H, N*H*), 12.84 (s, 1H, O*H*-8); ^{13}C NMR (δ) 122.7 *C1*, 133.3 *C2*, 132.4 *C3*, 118.8 *C4*, 156.3 *C4a*, 158.5 *C4b*, 95.2 *C5*, 164.2 *C6*, 99.4 *C7*, 162.6 *C8*, 102.7 *C8a*, 180.2 *C9*, 121.1 *C9a*, 135.8 *C10*, 143.0 *C1′*, 113.9 (*C2′* + *C6′*), 116.2 (*C3′* + *C5′*), 157.1 *C4′*. Anal. $C_{20}H_{13}FN_2O_4$ (C, H, N).

6.2. Mycology

6.2.1. Yeasts and culture medium

The antifungal activities against yeasts were determined by a conventional paper disk diffusion method [33]. Fungal growth inhibitory activity was evaluated on referenced strains obtained from the Institut Pasteur, Paris (*C. albicans* ATCC 10231 and *C. krusei* CBS 573). Strains were subcultured on casitone IP agar at 30 °C for 24 h.

6.2.2. Preparation of test samples

The compounds studied were dissolved in dimethylsulfoxide (DMSO), and serially diluted with the growth medium. Test disks (Bio-Rad, 6 mm in diameter) were sterilized in drying-room at 100 °C for 1 h, and were impregnated with 20 μL of an appropriate dilution. In preliminary assays, the applied amount of each substance were 100 μg/test disk; for compounds found to be active, further experiments were carried out with lower doses (50 μg and 25 μg/test disk). Impregnated disks were dried at 40 °C in a drying-room before use.

6.2.3. Disk diffusion method

A sterile aqueous suspension of the yeast (containing ca. 10^5 cells·mL^{-1}) was prepared from a 48-h primoculture incubated on Sabouraud's agar (Bio-Mérieux) as nutrient medium. For the experiments, the cell suspensions were controlled by direct count (Malassez chamber), and spread over the agar surface (10^3 cells) in Petri plates.

Test disks impregnated with the appropriate sample solution were applied on the plate surface, and the growth control was examined after a 24-h incubation at 30 °C. Results were expressed as the diameter (in mm) of the inhibition zone. For comparatives purposes, tests were performed with a standard antifungal drug (econazole, ICN Biomedicals Inc. USA); a control plate treated with a disk imbibed with the vehicle only (DMSO) was also included in the assays, as negative reference.

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References

[1] M. Bernabeu-Wittel, J.L. Villanueva, J. Pachon, A. Alarcon, L.F. Lopez-Cortes, P. Viciana, F. Cadaval, A. Talegon, Eur. J. Clin. Microbiol. Infect. Dis. 18 (1999) 324–329.
[2] R. Herbrecht, S. Neuville, V. Letscher-Bru, S. Natara-Ame, O. Lortholary, Drugs Aging 17 (2000) 339–351.
[3] J. Abbas, G.P. Bodey, H.A. Hanna, M. Mardini, E. Girgawy, D. Abi-Said, E. Whimbey, R. Hachem, I. Raad, Arch. Intern. Med. 160 (2000) 2659–2664.
[4] I. Jarque, S. Saavedra, G. Martin, J. Peman, C.P. Belles, M.A. Sanz, Haematologica 85 (2000) 441–443.
[5] R. Palacios, J. Santos, C. Romero, V. Garcia, A. Rivero, M. Marquez, Enferm. Infec. Microbiol. Clin. 17 (1999) 279–282.
[6] E.M. Johnson, D.W. Warnock, J. Luker, S.R. Porter, C. Scully, J. Antimicrob. Chemother. 35 (1995) 103–114.
[7] J. Baran Jr., E. Klauber, J. Barczak, K. Riederer, R. Khatib, J. Clin. Microbiol. 38 (2000) 870–871.
[8] C.R. Boschman, U.R. Bodnar, M.A. Tornatore, A.A. Obias, G.A. Noskin, K. Englund, M.A. Postelnick, T. Suriano, L.R. Peterson, Antimicrob. Agents Chemother. 42 (1998) 734–738.
[9] A. Gerber, C.A. Hitchcock, J.E. Swartz, F.S. Pullen, K.E. Marsden, K.J. Kwon-Chung, J.E. Bennett, Antimicrob. Agents Chemother. 39 (1995) 2708–2717.
[10] T.C. White, Antimicrob. Agents Chemother. 41 (1997) 1488–1494.
[11] D. Sanglard, F. Ischer, M. Monod, J. Bille, Microbiology 143 (1997) 405–416.
[12] S.K. Katiyar, T.D. Edlind, Med. Mycol. 39 (2001) 109–116.
[13] V.T. Andriole, Int. J. Antimicrob. Agents 16 (2000) 317–321.
[14] D.C.G. Pinto, N. Fuzzati, X.C. Pazmino, K. Hostettmann, Phytochemistry 37 (1994) 875–878.
[15] D.A. Garcia Cortez, M.C.M. Young, A. Marston, J.L. Wolfender, K. Hostettmann, Phytochemistry 47 (1998) 1367–1374.
[16] M. Chu, I. Truumees, R. Mierzwa, J. Terracciano, M. Patel, P.R. Das, M.S. Puar, T.M. Chan, Tetrahedron Lett. 39 (1998) 7649–7652.
[17] G. Rath, O. Potterat, S. Mavi, K. Hostettmann, Phytochemistry 43 (1996) 513–520.
[18] M. Palomba, G. Pintore, G. Boatto, B. Asproni, R. Cerri, A. Pau, G.A. Farris, Farmaco 51 (1996) 79–84.
[19] I.A. Shehata, M.N. Nasr, H.I. El-Subbagh, M.M. Gineinah, S.M. Kheira, Sci. Pharm. 64 (1996) 133–143.
[20] E. Ilhan, N. Ergenc, M. Kiraz, G. Otuk, Acta Pharm. Tur. 41 (1999) 111–115.
[21] P.K. Grover, G.D. Shah, R.C. Shah, J. Chem. Soc. (1955) 3982–3985.
[22] P.E. Eaton, G.R. Carlson, J.T. Lee, J. Org. Chem. 38 (1973) 4071–4073.
[23] J.A. Elix, H.W. Musidlak, T. Sala, M.V. Sargent, Aust. J. Chem. 31 (1978) 145–155.
[24] S.G. Küçükgüzel, S. Rollas, H. Erdeniz, M. Kiraz, Eur. J. Med. Chem. 34 (1999) 153–160.
[25] R.K.M. Pillai, P. Naiksatam, F. Johnson, R. Rajagopalan, P.C. Watts, R. Cricchio, S. Borras, J. Org. Chem. 51 (1986) 717–723.
[26] S. Huneck, G. Höfle, Tetrahedron 34 (1978) 2491–2502.

[27] E.E. Stinson, W.B. Wise, R.A. Moreau, A.J. Jurewicz, P.E. Pfeffer, Can. J. Chem. 64 (1986) 1590–1594.
[28] J.A. Elix, K.L. Gaul, H.T. Lumbsch, Aust. J. Chem. 40 (1987) 1031–1033.
[29] M. Chu, I. Truumees, R. Mierzwa, J. Terracciano, M. Patel, D. Loebenberg, J.J. Kaminski, P. Das, M.S. Puar, J. Nat. Prod. 60 (1997) 525–528.
[30] M. Pickert, A.W. Frahm, Arch. Pharm. Pharm. Med. Chem. 331 (1998) 177–192.
[31] C.T. Da Costa, J.J. Dalluge, M.J. Welch, B. Coxon, S.A. Margolis, D. Horton, J. Mass Spectrom. 35 (2000) 540–549.
[32] M. Scheven, L. Senf, Mycoses 37 (1994) 205–207.
[33] This product was previously prepared according to different experimental conditions ($POCl_3 + H_3PO_4 + ZnCl_2$) and was found to have a m.p. of 280 °C N.B. Nevrekar, S.V. Lele, M.V.R. Mucheli, N.A. Kudav, Chem. Ind. (1983) 479–480.
[34] D. Landini, F. Rolla, Chem. Ind. (1979) 213.