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LETTERS

Synthesis of novel 2-(3-aryl/alkylaminopropoxy)-12-arylxanthene derivatives as antifungal and antibacterial agents

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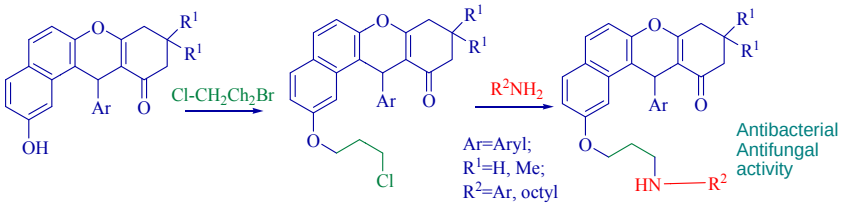
ABSTRACT



A series of novel 2-(3-aryl/alkylaminopropoxy)-12-aryl-9,10-dihydro-8*H*- benzo[*a*]xanthen-11-one derivatives were synthesized from 2-hydroxy-12-aryl 9,10-dihydro-8*H*-benzo[*a*]xanthen-11-ones by reaction with 1-bromo-3-chloropropane in presence of K_2CO_3 in dry acetone under reflux followed by reaction with aryl/alkyl amines in presence of KI in dry DMF at 100°C. Structures have been confirmed by spectroscopic analysis. All the newly synthesized 2-(3- aryl/alkylaminopropoxy)-12-aryl xanthene derivatives were screened for their antimicrobial activity against four microbial strains *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*. The selected synthesized compounds showed moderate antimicrobial activity.

Keywords: Biological activity, xanthene derivatives, diversity, condensation, strains

INTRODUCTION

Antimicrobial resistance threatens the continuation of existing antimicrobial drugs. Microorganisms are evolving at an alarming rate and developing resistance to existing drug molecules. The increasing drug resistance has challenged the efficacy of the existing drugs and thus causing a vaccum of antimicrobial drugs.[1] Excessive and widespread use of antibiotics in the past few decades is also a contributing factor to the development of bacterial drug resistance. With Gram-positive bacteria, many drug resistant strains including methicillin-resistant *Staphylococcous aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumonia* (PRSP) and vancomycin-resistant *Enterococci* (VRE) are posing a serious threat.[2,3] Thus, it has become imperative to synthesize new types of antibacterial drugs having higher efficiency and new targets or mechanisms to achieve antimicrobial effects.

Heterocycles are well known to display a wide array of biological activities.[4] Xanthenes are tricyclic dibenzopyran derivatives with diverse applications in laser technology,[5] dyes[6] and pH sensitive fluorescent materials.[7] Xanthenes are also biologically significant motifs as they exhibit a variety of pharmacological activities such as antibacterial and antifungal, (Figure 1)[8,9] antioxidant,[10] antileukemic,[11] insecticidal,[12] antiplasmodial and antitumor,[13] antimycobacterial,[14] antiviral,[15] anti-inflammatory[16] and antimalarial.[17] Xanthene scaffold is also reported to be β Site Amyloid Precursor Protein Cleaving Enzyme (BACE1) Inhibitor.[18] A series of epoxypropoxy-substituted xanthene derivatives which display significant cytotoxic, topoisomerase inhibition and DNA cross-linking activities have also been reported.[19-21] Due to the planar structure of the xanthone, its anticancer activity was related with its interaction with DNA. This mechanism of action suggests

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that the planar structure of xanthene derivative interacts with DNA, perhaps through intercalation, directing the reactive epoxides to the site of alkylation and can be dramatically altered by the ring substituents and their positions.[22] Furthermore, organic and heterocyclic moieties functionalized with aminoalkoxy linkages are known to act as antidepressants and potential antipsychotics[23-25]

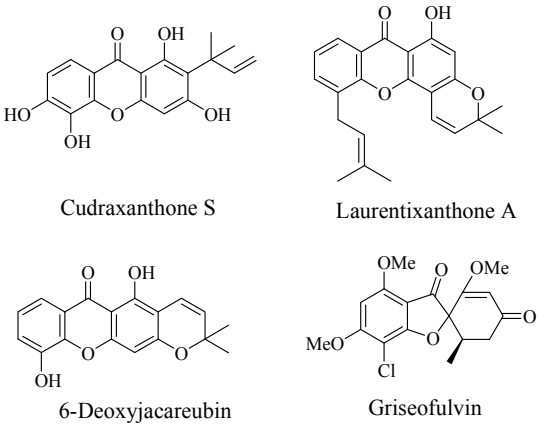


Figure 1. Biologically active xanthenes drug derivatives.

Several effective bacterial membrane-targeting small molecules with promising membrane selectivity have been synthesized using xanthone as a template. A series of nonpeptidicamphiphilic amino alkoxyxanthone derivatives have been reported for targeting the bacterial cytoplasmic membrane[26] and 3,6-bis-ω-diethylaminoalkoxyxanthones have been reported to show promising *in vitro* activity against strains of chloroquine-susceptible and multidrug-resistant Plasmodium falciparum.[27]

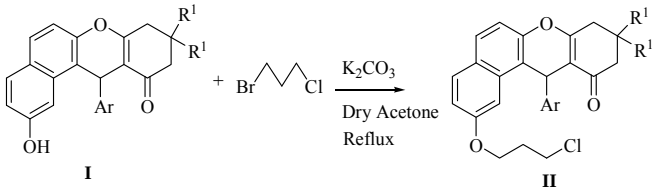
In view of the importance of xanthenes and amino alkoxy side chains, we herein report the synthesis of a series of 2-(3-aryl/alkylaminopropoxy)-12-aryl xanthene derivatives from 2-hydroxy-12-aryl xanthenes by a two steps sequence involving alkylation of xanthenes with 1-bromo-3-chloropropane followed by amination with aryl/alkyl amines and further investigation of their biological applications.

RESULTS AND DISCUSSION

Chemistry

We have synthesized a series of novel 2-(3-alkyl/arylamino propoxy)-12-aryl-9,10,dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives (IIIa-IIIp) from 2-hydroxy-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-ones by a two steps sequence involving reaction with 1-bromo-3-chloropropane in presence of K_2CO_3 in dry acetone followed by amination with aryl/alkyl amines in dry DMF in presence of KI at 100 °C.

The starting 2-hydroxy-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-ones (I) were prepared by the three component condensation of aromatic aldehydes, 2,7-dihydroxy naphthalene and dimedone/cyclohexa-1,3-dione using *p*TSA as catalyst in ethanol under reflux.[28] Further, 12-aryl-2-(3-chloropropoxy)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*] xanthen-11-one derivatives (IIa-IIn) were synthesized by reaction of 2-hydroxy-12-aryl-9,10-dihydro-8*H*-benzo[*a*] xanthen-11-ones (I) with 1-bromo-3-chloropropane in dry acetone in presence of K_2CO_3 at 60°C (Scheme 1). The results are listed in Table 1. All the products were identified by IR, ^{1}H NMR, ^{13}CNMR and mass spectra.



Scheme 1.Synthesis of 2-(3-chloropropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives

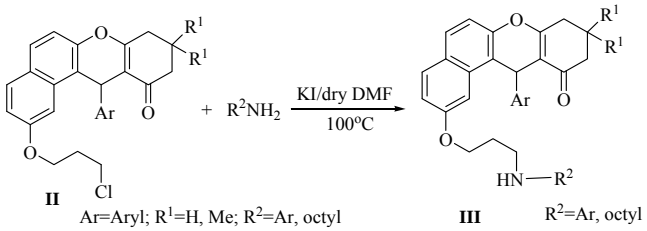
Finally, the target compounds 2-(3-alkyl/arylamino propoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives

Table 1: Synthesis of 2-(3-chloropropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives (IIa-n)

Entry	Ar	R^1	Product (II)	Time (h)	Yield (%)
1.	4-FC_6H_4	CH_3	**IIa**	5	73
2.	4-MeC_6H_4	CH_3	**IIb**	5	96
3.	3-$(O_2N)C_6H_4$	CH_3	**IIc**	5	89
4.	3-BrC_6H_4	CH_3	**IId**	4.5	88
5.	4-BrC_6H_4	CH_3	**IIe**	4	77
6.	2-Naphthyl	CH_3	**IIf**	6	88
7.	4-$(MeO)C_6H_4$	CH_3	**IIg**	6	88
8.	4-ClC_6H_4	CH_3	**IIh**	6	85
9	4-$(O_2N)C_6H_4$	CH_3	**IIi**	4	89
10.	4-MeC_6H_4	H	**IIj**	12	86
1.	4-$(O_2N)C_6H_4$	H	**IIk**	6	86
12.	4-$(MeO)C_6H_4$	H	**IIl**	15	82
13.	4-BrC_6H_4	H	**IIm**	12	88
14.	4-FC_6H_4	H	**IIn**	10	89

(IIIa-p) were synthesized by the reaction of 12-aryl-2- (3-chloropropoxy)- 9,10-dihydro- 8H-benzo[*a*] xanthen-11-one derivatives (IIa-n) with aryl/alkyl amines in presence of KI in dry DMF at 100 °C (Scheme 2). The addition of KI enhances rate of nucleophilic substitution reaction. All the products were obtained in high yields and the results are summarized in Table 2. The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra.

IR spectra of the compound **IIIl** showed characteristic N-H and C=O stretch at 3392 cm^{-1} and 1645 cm^{-1}, respectively. The ^{1}H NMR spectrum of **IIIl** revealed thirteen aromatic protons in the range of δ 7.66-6.60. The methine proton appeared as sharp singlet at δ 5.55. One sharp singlet appeared at δ 3.57for N-H proton (confirmed by D_2O exchange). Two CH_2 group protons showed two multiplets at δ4.19-4.14 and δ 4.07-3.96 for each



Scheme 2. Synthesis of 2-(3-alkyl/arylaminopropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*] xanthen-11-one derivatives

proton and one sharp singlet appeared at 3.75 for OCH_3 group protons. Other CH_2 and CH_3groups appeared in the range at δ 3.31-1.94. Further, the off-resonance decoupled ^{13}C NMR spectrum of **IIII** showed signal at δ 34.58 for one methine carbon and at δ 65.87, 28.88, 42.17, 27.68, 20.26 and 37.00, for six methylene carbons. Two methylcarbons showed two signals at δ 20.96 and δ 55.80 and the carbonyl carbon appeared at δ 197.19. Twenty two aromatic carbons and two enolic carbons appeared in the range of δ 103.32-165.46. The position of peaks of methyl, methylene, and methine carbons were assigned by DEPT spectra of compound **IIII**. The two-dimensional NMR spectra of HMBC and COSY correlations are useful in the signal assignment of **IIII** and various characteristic signals are shown in figure 2. The mass spectrum of compound **IIII** showed a molecular ion peak at m/z 519.2202 $[M]^+$.

Pharmacology

All the synthesized 2-(3-alkyl/arylaminopropoxy)-12-aryl xanthene derivatives were analyzed for their antibacterial activity. All the tested 2-(3- aryl/alkylaminopropoxy)-12-aryl xanthene derivatives showed variable antibacterial activity against the Gram-positive (*Staphylococcus aureus and Bacillus*

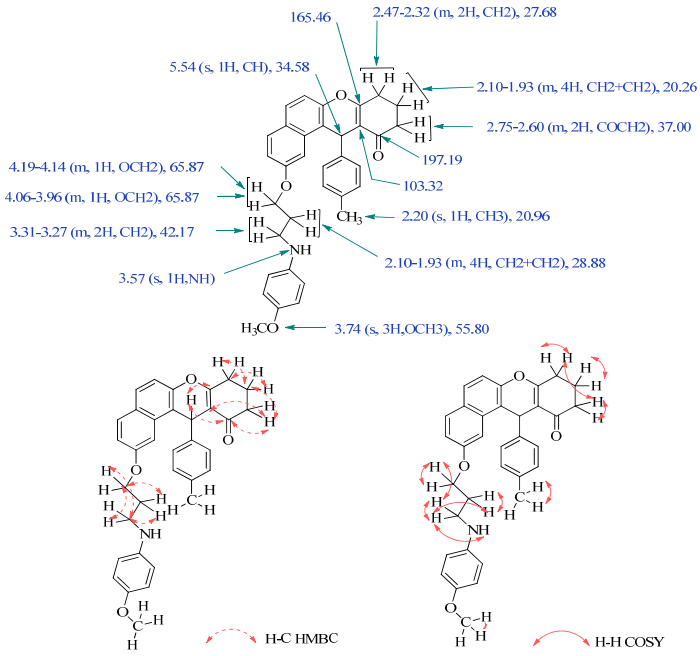


Figure 2: HMBC and COSY correlations of **IIII** and various characteristic ^1H and ^{13}C NMR peaks

subtilis) and Gram-negative bacteria (*Pseudomonas aeruginosa*) except Gram-negative (*Escherichia coli*) bacteria. Positive controls produced significantly sized inhibition zones against the tested bacteria. However, negative control produced no inhibitory effect against any of the test organism as shown in Table 3.

On the basis of maximum inhibitory activity shown against

Table 2: Synthesis of 2-(3-alkyl/arylaminopropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*] xanthen-11-one derivatives (IIIa-p)

Entry	Ar	R^1	R^2	Product (III)	Time (h)	Yield (%)
1.	4-FC_6H_4	CH_3	4-$(MeO)C_6H_4$	**IIIa**	4.5	87
2.	4-MeC_6H_4	CH_3	4-MeC_6H_4	**IIIb**	4.5	88
3.	3-$(O_2N)C_6H_4$	CH_3	4-MeC_6H_4	**IIIc**	5	81
4.	3-BrC_6H_4	CH_3	4-$(MeO)C_6H_4$	**IIId**	4	88
5.	4-BrC_6H_4	CH_3	4-FC_6H_4	**IIIe**	4	83
6.	2-Naphthyl	CH_3	4-MeC_6H_4	**IIIf**	6	80
7.	4-$(MeO)C_6H_4$	CH_3	$(CH_2)_7CH_3$	**IIIg**	4.5	83
8.	4-ClC_6H_4	CH_3	4-MeC_6H_4	**IIIh**	4	89
9.	4-$(O_2N)C_6H_4$	CH_3	4-FC_6H_4	**IIIi**	4	89
10.	4-$(MeO)C_6H_4$	CH_3	4-MeC_6H_4	**IIIj**	4.5	85
11.	3-BrC_6H_4	CH_3	4-MeC_6H_4	**IIIk**	4	86
12.	4-MeC_6H_4	H	4-$(MeO)C_6H_4$	**IIIl**	8	79
13.	4-$(O_2N)C_6H_4$	H	4-MeC_6H_4	**IIIm**	8	75
14.	4-$(MeO)C_6H_4$	H	4-MeC_6H_4	**IIIn**	7	83
15.	4-BrC_6H_4	H	4-$(MeO)C_6H_4$	**IIIo**	8	77
16.	4-FC_6H_4	H	4-$(MeO)C_6H_4$	**IIIp**	5	78

Gram positive bacteria, three compounds namely, **IIIg**, **IIIi&IIId** were found to be most effective against *B. subtilis* with zone of inhibition of 25 mm and compound **IIIg** displayed zone of inhibition of 19.3 mm against *S. aureus* whereas in case of Gram negative bacteria, compounds **IIIg** & **IIIb** displayed zone of inhibition of 14 mm against *P. aeruginosa* (Table 3). Graphical representation of diameter of growth of inhibition (mm) of 2-(3-alkyl/arylaminopropoxy)-12-aryl-9,10-dihydro-8*H*-benzo [*a*]xanthen-11-one derivatives (III) against bacteria and yeast strains is shown in Figure 3.

Table 3: Antibacterial activity of 2-(3-alkyl/arylaminopropoxy)-2-aryl xanthene derivatives through agar well diffusion method

Comp.	Diameter of growth of inhibition zone (mm)a			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
IIIa	13.0±0	20.6±0.57	-	12.3±0.57
IIIb	15.6±0.57	20.6±0.57	-	14.3±0.57
IIIc	12.6±0.57	16.6±0.57	-	12.3±0.57
IIId	16.3±0.57	25.3±0.57	-	13.6±0.57
IIIe	13.6±0.57	21.3±0.57	-	12.6±0.57
IIIf	16.6±0.57	24.6±0.57	-	12.6±0.57
IIIg	19.3±0.57	25.3±0.57	-	14.3±0.57
IIIh	12.6±0.57	20.6±0.57	-	13.6±0.57
IIIi	17.3±0.57	25.6±0.57	-	13.6±0.57
IIIj	12.0±1	19.3±0.57	-	12.3±0.57
IIIk	14.3±0.57	23.0±1	-	12.6±0.57
IIIl	12.0±1	12.3±0.57	-	-
IIIm	11.6±0.57	12.6±0.57	-	-
IIIn	11.3±0.57	13.6±0.57	-	-
IIIo	13.3±0.57	15.0±1	-	-
IIIp	13.6±0.57	14.3±0.57	-	-
Ciproflo xacin	26.6±0.57	24.0±0	25.0±0	22.0±1

- No activity; [a]Values, including diameter of the well (8mm), are means of three replicates

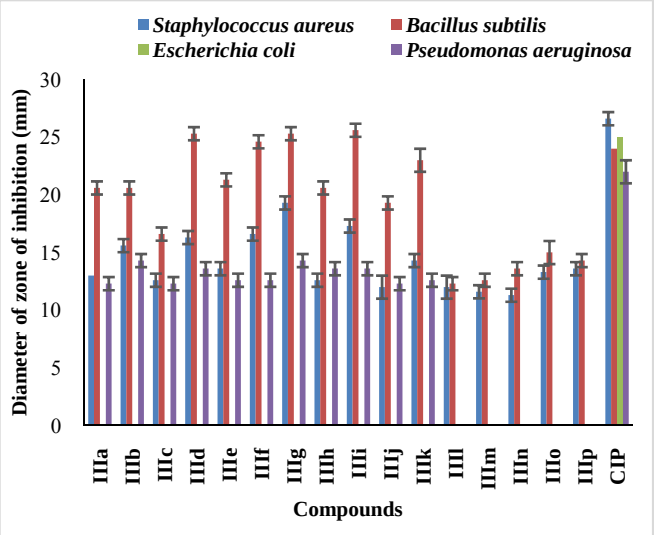


Figure 3: Diameterof growth of inhibition (mm) of 2-(3-alkyl/arylaminopropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*] xanthen-11-one derivatives (III) against bacteria and yeast strains

EXPERIMENTAL

All the reagents and solvents were commercially available and used as received. Thin layer chromatography (GF254) was used to monitor reaction progress. Melting points were measured on Buchi M-560 melting point apparatus and are uncorrected. IR ($CHCl_3$) spectra were recorded on Perkin Elmer FTIR spectrophotometer and values are expressed in ν_{max} (cm^{-1}). The ^1H NMR and ^{13}C NMR spectra were recorded on Jeol JNM ECX-400P at 400 and 100 MHz respectively, using TMS as internal standard. The chemical shift values are recorded on δ scale. Mass spectral data were recorded on Agilent 6200 QT of (ESI-HRMS) Mass Spectrometer. Xanthenes (1) were prepared by condensation of cyclic 1,3-diketones, aromatic aldehydes and 2,7-dihydroxynapthalene according to the reported method.[28]

General procedure for the synthesis of 12-aryl-2-(3-chloropropoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives (IIa-IIn)

A mixture of xanthene 1 (1.0 mmol) and 1-bromo-3-chloropropane (1.0 mmol) in 3 mL of acetone was heated under reflux in the presence of catalytic amount of K_2CO_3 (10 mol%) for the appropriate time as mentioned in Table 1. The progress of the reaction was monitored by TLC using ethyl acetate:petroleum ether (30:70, v/v) as eluent. After completion of the reaction, the reaction mixture was filtered and washed with acetone. The acetone was removed on rotary evaporator and the solid obtained was dried under vaccum. All the products were characterized by IR, ^1H NMR, ^{13}C NMR and mass spectra.

2-(3-Chloropropoxy)-12-(4-fluorophenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIa)

White solid; Yield = 73%; M.p.=198 °C; IR (KBr) ν_{max}, cm^{-1}: 2961, 1652, 1622, 1373, 1224; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J*=7.2Hz, 2H, Ar), 7.34 (m, 2H, Ar), 7.18 (m, 2H, Ar), 7.00 (d, *J* =8.7 Hz, 1H, Ar), 6.89 (t, *J*=8.55 Hz, 2H, Ar), 5.56 (s, 1H,CH), 4.18 (m, 1H, OCH_2), 4.05 (m, 1H, OCH_2), 3.75 (m, 2H, CH_2Cl), 2.57 (s, 2H, CH_2CO), 2.35 (m, 4H, CH_2CMe_2 + CH_2CH_2Cl), 1.12 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}CNMR (300 MHz, $CDCl_3$): 196.97, 163.85, 157.54, 148.23, 140.52, 140.47, 132.64, 130.00, 129.98, 129.89, 128.63, 126.82, 117.50, 116.39, 115.19, 114.90, 114.56, 113.96, 103.45, 64.29, 50.87, 41.44, 41.39, 34.39, 32.24, 32.06, 29.29, 27.11; HRMS (ESI) $[M+H]^+$ Calc. for $C_{28}H_{26}ClFO_3$:465.1633, found: $[M+H]^+$465.1641, 467.1622 $[M+H+2]^+$.

2-(3-Chloropropoxy)-9,9-dimethyl-12-(4-methyl)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11 (12*H*)-one (IIb)

White solid; Yield=86%, M.p.=167°C, IR (KBr) ν_{max},cm^{-1}: 2961, 2943, 1648, 1602, 1375, 1223; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H, Ar), 7.27-7.24 (m, 3H, Ar), 7.16 (d, *J*=6.6Hz, 1H, Ar), 6.99-6.98 (m, 1H, Ar), 5.53 (s, 1H, CH), 4.24-4.18 (m, 1H, OCH_2), 4.08-4.03 (m, 1H, OCH_2), 3.76-3.71 (m, 2H, CH_2Cl), 2.57 (s, 2H, CH_2CO), 2.33-2.21 (m, 4H, CH_2CO + CH_2CH_2Cl), 1.12 (s, 3H, CMe), 0.98 (s, 3H, CMe). ^{13}C NMR (300 MHz, $CDCl_3$): 197.08, 163.62, 157.85, 157.44, 148.16, 137.11, 132.78, 129.89, 129.46, 128.35, 126.81, 117.45,

116.93, 114.57, 114.28, 113.62, 103.58, 64.30, 55.11, 50.93, 41.52, 41.42, 34.29, 32.27, 32.13, 29.29, 27.24; HRMS (ESI) [M+H]+ Calc. for $C_{29}H_{29}ClO_3$: 461.1883, found: $[M+H]^+$461.1859, 463.1696 $[M+H+2]^+$.

2-(3-Chloropropoxy)-9,9-dimethyl-12-(3-nitrophenyl)-9,10-dihydro-8*H*-benzo [*a*]xanthen-11(12*H*)-one (IIc)

White solid; Yield = 89%; M.p.=156°C; IR (KBr) ν_{max}, cm^{-1}: 2961, 2924, 1655, 1621, 1352, 1224; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H, Ar), 7.96-7.93 (m, 1H, Ar), 7.79-7.68 (m, 3H, Ar), 7.40-7.35 (m, 1H, Ar), 7.26-7.19 (m, 2H, Ar), 7.14-7.13(m, 1H, Ar), 7.03 (dd, *J*=2.25 Hz, *J*=8.85 Hz, 1H, Ar), 5.68 (s, 1H, CH), 4.26 (m, 1H, OCH_2), 4.03 (m, 1H, OCH_2), 3.77 (m, 2H, CH_2Cl), 2.62 (s, 2H, CH_2CO), 2.37 (m, 4H, CH_2CO + CH_2CH_2Cl), 1.14 (s, 3H, CMe), 0.97 (s, 3H, CMe); ^{13}C NMR (300 MHz, $CDCl_3$): 196.86, 164.55, 157.79, 148.35, 148.23, 146.76, 134.71, 132.33, 130.20, 129.23, 129.06, 126.84,123.23, 121.61, 117.63, 115.08, 114.69, 113.00, 102.99, 64.35, 50.72, 41.35, 35.15, 32.30, 32.03, 29.23, 27.17; HRMS (ESI) $[M+H]^+$ Calc. for $C_{28}H_{26}ClNO_5$: 492.1578, found: $[M+H]^+$492.1539, 494.1523 $[M+H+2]^+$.

12-(3-Bromophenyl)-2-(3-chloropropoxy)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12H)-one (IId)

White solid; Yield = 88%; M.p.=176°C; IR (KBr) ν_{max}, cm^{-1}: 2956, 1652, 1620, 1375, 1223; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (dd, *J*=3.75 Hz, *J*=8.75 Hz, 2H, Ar), 7.48 (s, 1H, Ar), 7.32 (m, 1H, Ar), 7.21 (m,3H, Ar), 7.08 (m, 1H, Ar), 7.03 (m, 1H, Ar), 5.52 (s, 1H, CH), 4.26 (m, 1H, OCH_2), 4.07 (m, 1H, OCH_2), 3.78 (m, 2H, CH_2Cl), 2.59 (s, 2H, CH_2CO), 2.35 (m, 4H, CH_2CMe_2 + CH_2CH_2Cl), 1.13 (s, 3H, CMe), 0.99 (s, 3H, CMe); ^{13}C NMR (300 MHz, $CDCl_3$): 196.81, 164.09, 157.60, 148.15, 146.96, 132.59, 131.61, 129.99, 129.77, 129.52, 128.81, 127.29, 126.80, 122.40, 117.64, 115.86, 114.59, 113.47, 103.29, 98.52, 64.38, 50.82, 41.43, 35.06, 32.29, 32.09, 29.21, 27.26. HRMS (ESI) $[M+H]^+$ Calc. for $C_{28}H_{26}BrClO_3$: 525.0832, found: $[M+H]^+$, 525.0856, 527.0847 $[M+H+2]^+$.

12-(4-Bromophenyl)-2-(3-chloropropoxy)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIe)

White solid; Yield = 77%; M.p.=178°C; IR (KBr) ν_{max}, cm^{-1}: 2962, 1650, 1602, 1375, 1222; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.65 (m, 2H, Ar), 7.31-7.29 (m, 2H, Ar), 7.26-7.22 (m, 2H, Ar), 7.18-7.14 (m, 2H, Ar), 7.01 (dd, *J*=3.9 Hz, *J*=6.75 Hz, 1H, Ar), 5.53 (s, 1H, CH), 4.22-4.16 (m, 1H, OCH_2), 4.04-4.00 (m, 1H, OCH_2), 3.76-3.72 (m, 2H, CH_2Cl), 2.56 (s, 2H, CH_2CO), 2.33-2.22 (m, 4H, CH_2CMe_2 + CH_2CH_2Cl), 1.12 (s, 3H, CMe), 0.96 (s, 3H, CMe). ^{13}C NMR (300 MHz, $CDCl_3$): 196.81, 164.09, 157.60, 148.15, 146.96, 132.59, 131.61, 129.99, 129.77, 129.52, 128.81, 127.29, 126.80, 122.40, 117.64, 115.86, 114.59, 113.47, 103.29, 98.52, 64.38, 50.82, 41.43, 35.06, 32.29, 32.09, 29.21, 27.26. HRMS (ESI) $[M+H]^+$ Calc. for $C_{28}H_{26}BrClO_3$: 525.0832, found: $[M+H]^+$525.085, 527.0834 $[M+H+2]^+$.

2-(3-Chloropropoxy)-9,9-dimethyl-12-(naphthalen-2-yl)-9,10-dihydro-8*H*-benzo[*a*]xanthen- 11(12*H*)-one (IIf)

White solid; Yield = 88%; M.p.=184°C; IR (KBr) ν_{max}, cm^{-1}: 2959, 2926, 1650, 1621, 1374, 1222; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (s, 1H, Ar), 7.75-7.62 (m, 5H, Ar), 7.48-7.45 (m,1H, Ar), 7.40-7.32 (m, 3H, Ar), 7.25-7.19 (m, 1H, Ar), 6.95 (dd, *J*= 2.25 Hz, 8.85 Hz, 1H, Ar), 5.74 (s, 1H, CH), 4.21 (m, 1H, OCH_2), 4.00 (m, 1H, OCH_2), 3.71 (m, 2H, CH_2Cl), 2.59 (s, 2H, CH_2CO), 2.33 (m, 1H, CH_2CMe_2), 2.23 (m, 3H, CH2CMe_2+CH_2CH_2), 1.11 (s, 3H, CMe), 0.94 (s, 3H, CMe); ^{13}C NMR (300 MHz, $CDCl_3$): 196.95, 163.92, 157.47, 148.25, 142.09, 133.31, 132.84, 132.17, 129.91, 128.61, 128.07, 127.88, 127.47, 127.28, 126.81, 125.87, 125.49, 117.52, 116.60, 114.60, 113.90, 103.55, 64.36, 50.91, 41.47, 35.42, 32.26, 32.08, 29.32, 27.24; HRMS (ESI) $[M+H]^+$ Calc. for $C_{32}H_{29}ClO_3$: 497.1883, found: $[M+H]^+$ 497.1892, 499.1876 $[M+H+2]^+$.

2-(3-Chloropropoxy)-12-(4-methoxyphenyl)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*] xanthen-11(12*H*)-one (IIg)

White solid; Yield = 88%; M.p.=158°C (decom.); IR (KBr) ν_{max}, cm^{-1}: 2958, 2927, 1654,1622, 1377, 1222; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 9.0 Hz, 2H, Ar), 7.27-7.25 (m, 3H, Ar), 7.16 (d, *J*=9 Hz, 1H, Ar), 6.99 (dd, *J* = 2.4 Hz, *J* = 9.0 Hz, 1H, Ar), 6.71 (d, *J*=9 Hz, 2H, Ar), 5.51 (s, 1H, CH), 4.21 (m, 1H, OCH_2), 4.08 (m, 1H, OCH_2), 3.77 (m, 2H, CH_2Cl), 3.69 (s, 3H, OCH_3), 2.56 (s, 2H, CH_2CO), 2.34 (m, 4H, CH_2CMe_2+CH_2CH_2Cl), 1.12 (s, 3H, CMe), 0.98 (s, 3H, CMe); ^{13}C NMR (300 MHz, $CDCl_3$): 197.08, 163.62, 157.85, 157.44, 148.16, 137.11, 132.78, 129.89, 129.46, 128.35, 126.81, 117.45, 116.93, 114.57, 114.28, 113.62, 103.58, 64.30, 55.11, 50.93, 41.52, 41.42, 34.29, 32.27, 32.13, 29.29, 27.24; HRMS (ESI) $[M+H]^+$ Calc. for $C_{29}H_{29}ClO_4$: 477.1833, found: $[M+H]^+$477.1797, 479.1786 $[M+H+2]^+$.

12-(4-Chlorophenyl)-2-(3-chloropropoxy)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen- 11(12*H*)-one (IIh)

White solid; Yield = 85%; M.p.=163°C; IR (KBr) ν_{max}, cm^{-1}: 2963, 2929, 1651, 1622, 1376, 1222; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J*=6.9 Hz, 2H, Ar), 7.26 (m, 3H, Ar), 7.16 (m, 1H, Ar), 6.98 (dd, *J* =1.2 Hz, *J* =6.6 Hz, 1H, Ar), 6.70(d, *J*=6.3 Hz, 2H, Ar), 5.50 (s, 1H,CH), 4.21 (m, 1H, OCH_2), 4.05 (m, 1H, OCH_2), 3.73 (m, 2H, CH_2Cl), 2.55 (s, 2H, CH_2CO), 2.25 (m, 4H, CCH_2+ CH_2CH_2), 1.11 (s, 3H, CMe), 0.97 (s, 3H, CMe). ^{13}CNMR (300 MHz, $CDCl_3$): 196.97, 163.85, 157.54, 148.23, 140.52, 140.47, 132.64, 130.00, 129.98, 129.89, 128.63, 126.82, 117.50, 116.39, 115.19, 114.90, 114.56, 113.96, 103.45, 64.29, 50.87, 41.44, 41.39, 34.39, 32.24, 32.06, 29.29, 27.11. HRMS (ESI) $[M+H]^+$ Calc. for $C_{28}H_{26}Cl_2O_3$: 481.1337, found: $[M+H]^+$481.1301, 483.1687 $[M+H+2]^+$.

2-(3-Chloropropoxy)-12-(4-nitrophenyl)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIi)

White solid; Yield = 89%; M.p.=217°C; IR (KBr) ν_{max}, cm^{-1}: 2964, 1651, 1621, 1345, 1228; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08-8.02 (m, 2H, Ar), 7.71-7.66 (m, 2H, Ar), 7.52-7.49 (m, 2H, Ar), 7.19-7.17 (m, 1H, Ar), 7.06-6.99 (m, 2H, Ar), 5.66 (s, 1H, CH), 4.19-4.14 (m, 1H, OCH_2), 4.00-3.96 (m, 1H, OCH_2), 3.73-3.69 (m, 2H, CH_2Cl), 2.58-2.57 (m, 2H, CH_2CO), 2.33-2.15 (m, 4H, CH_2CO + CH_2CH_2Cl), 1.11 (s, 3H, CMe), 0.93 (s, 3H, CMe); ^{13}C NMR (300 MHz, $CDCl_3$): 196.77, 164.58, 157.75, 151.82,148.23, 146.31, 130.14, 129.33, 129.19, 123.56, 117.52, 114.99, 114.54, 112.82, 103.07, 64.25, 50.68, 41.34, 35.12, 32.19, 31.96, 29.22, 27.01; HRMS (ESI) $[M+H]^+$ Calc. for $C_{28}H_{26}ClNO_5$: 492.1578, found: $[M+H]^+$ 492.1580, 494.1567 $[M+H+2]^+$.

2-(3-Chloropropoxy)-12-(4-methyl)-9,10-dihydro-8*H*-benzo[*a*] xanthen-11(12*H*)-one (IIj)

White solid; Yield = 86%; M.p.=217°C; IR (KBr) ν_{max}, cm^{-1}: 2922, 1652, 1619, 1372, 1225; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, *J*=2.25 Hz, *J*=8.85 Hz, 2H, Ar), 7.26-7.22 (m, 3H, Ar), 7.16 (d, *J*=8.7 Hz, 1H, Ar), 7.00-6.97 (m,3H, Ar), 5.55 (s, 1H, CH), 4.23-4.16 (m, 1H, OCH_2), 4.06-3.99 (m, 1H, OCH_2), 3.75-3.68 (m, 2H, CH_2Cl), 2.77-2.62 (m, 2H, CH_2CO), 2.48-2.31 (m, 2H, CH_2CH_2), 2.27-2.17 (m, 5H, CMe+CH_2CH_2), 2.09-2.08 (m, 2H, CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.13, 165.38, 157.39, 148.14, 142.10, 135.78, 132.75, 129.84, 128.96, 128.43, 128.33, 126.76, 117.42, 116.91, 115.54, 114.47, 103.50, 64.23, 41.48, 37.04, 34.67, 32.09, 27.72, 20.98, 20.30; HRMS (ESI) $[M+H]^+$ Calc. for $C_{27}H_{25}ClO_3$: 433.1570, found: $[M+H]^+$433.1598, 435.1583 $[M+H+2]^+$.

2-(3-Chloropropoxy)-12-(4-nitrophenyl)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIk)

White solid; Yield = 86%; M.p.=230°C; IR (KBr) ν_{max}, cm^{-1}: 2946, 1653, 1619, 1345, 1224; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J*=8.7 Hz, 2H, Ar), 7.74 (t, *J*=9.3 Hz, 2H, Ar), 7.52 (d, *J*=8.7 Hz, 2H, Ar), 7.26 (m, 1H, Ar), 7.05 (m, 2H, Ar), 5.71 (s, 1H, CH), 4.22 (m, 1H, OCH2), 4.01 (m, 1H, OCH_2), 3.77 (m, 2H, CH_2Cl), 2.80 (m, 2H, CH_2CO), 2.49 (m, 2H, CH_2CH_2), 2.28 (m, 2H, CH_2CH_2), 2.13 (m, 2H, CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 196.67, 166.30, 157.83, 152.12, 148.32, 146.42, 132.44, 130.20, 129.46, 129.26, 126.88, 123.66, 117.58, 115.10, 114.54, 114.20, 103.20, 64.33, 41.39, 36.94, 35.16, 32.04, 27.79, 20.26; HRMS (ESI) $[M+H]^+$ Calc. for $C_{26}H_{22}ClNO_5$: 464.1265, found: $[M+H]^+$464.1276, 466.1257 $[M+H+2]^+$.

2-(3-Chloropropoxy)-12-(4-methoxyphenyl)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIl)

White solid; Yield = 82%; M.p.=186°C; IR (KBr) ν_{max}, cm^{-1}: 2954, 2927, 1652, 1619, 1374, 1226; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=8.7 Hz, 2H, Ar), 7.27-7.24 (m, 2H, Ar), 7.21-7.15 (m, 2H, Ar), 6.99 (dd, *J*=2.25 Hz, *J*=8.85 Hz, 1H, Ar), 6.71 (d, *J*=8.4 Hz, 2H, Ar), 5.54 (s, 1H, CH), 4.23 (m, 1H, OCH_2), 4.06 (m, 1H, OCH_2), 3.77-3.69 (m, 5H, CH_2Cl+OMe), 2.77 (m, 2H, CH_2CO), 2.49 (m, 2H, CH_2CH_2), 2.27 (m, 2H, CH_2CH_2), 2.08 (M, 2H, CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.23, 165.32, 157.90, 157.42, 148.18, 137.39, 132.76, 129.88, 129.54, 128.36, 126.80, 117.43, 116.94, 115.60, 114.50, 113.65, 103.62, 64.30, 55.13, 41.51, 37.08, 34.24, 32.12, 27.74, 20.36; HRMS (ESI) $[M+H]^+$ Calc. for $C_{27}H_{25}ClO_4$: 449.1520, found: $[M+H]^+$ 449.1501, 451.1533 $[M+H+2]^+$.

12-(4-Bromophenyl)-2-(3-chloropropoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIm)

White solid; Yield = 88%; M.p.=227°C; IR (KBr) ν_{max}, cm^{-1}: 2950, 1654, 1618, 1372, 1224; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (m, 2H, Ar), 7.31-7.12 (m, 6H, Ar), 7.01 (d, *J*=6.3 Hz, 1H, Ar), 5.56 (s, 1H, CH), 4.21-4.16 (m, 1H, OCH_2), 4.03-3.98 (m, 1H, OCH_2), 3.75-3.72 (m, 2H, CH_2Cl), 2.76-2.66 (m, 2H, CH_2CO), 2.48-2.38 (m, 2H, CH_2CH_2), 2.26-2.17 (m, 2H, CH_2CH_2), 2.08-1.97 (m, 2H, CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.14, 165.72, 157.50, 148.14, 143.93, 131.32, 129.95, 128.71, 117.45, 114.84, 103.28, 64.19, 41.44, 36.93, 34.54, 31.98, 27.67, 20.22; HRMS (ESI) $[M+H]^+$ Calc. for $C_{26}H_{22}BrClO_3$: 497.0519, found: [M+H]+497.0516, 499.0485 $[M+H+2]^+$.

2-(3-Chloropropoxy)-12-(4-fluorophenyl)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIn)

White solid; Yield = 89%; M.p.=174°C; IR (KBr) ν_{max}, cm^{-1}: 2954, 1653, 1619, 1373, 1225; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H, Ar), 7.33-7.26 (m, 3H, Ar), 7.19-7.14 (m, 1H, Ar), 7.01 (dd, *J*=2.25 Hz, *J*=8.85 Hz, 1H, Ar), 6.89 (t, *J*=8.7 Hz, 2H, CH), 5.58 (s, 1H, CH), 4.22 (m, 1H, OCH_2), 4.03 (m, 1H, OCH_2), 3.77 (m, 2H, CH_2Cl), 2.77 (m, 2H, CH_2CO), 2.49 (m, 2H, CH_2CH_2), 2.34 (m, 2H, CH_2CH_2), 2.23 (m, 2H, CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.19, 165.60, 157.54, 148.23, 140.76, 132.63, 130.09, 129.99, 128.65, 126.82, 117.50, 116.41, 115.23, 114.95, 114.51, 103.47, 64.28, 41.47, 37.04, 34.36, 32.06, 27.74, 20.32; HRMS (ESI) $[M+H]^+$ Calc. for $C_{26}H_{22}ClFO_3$: 437.1320, found: $[M+H]^+$437.1315, 439.1293 $[M+H+2]^+$.

General procedure for the synthesis of 2-(3-alkyl/arylaminopropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives (IIIa-p)

2-(3-Chloropropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one (II) (1.0 mmol) was taken in 10 mL of dry DMF in a round bottom flask. Amine (1.25 mmol) and potassium iodide (2.5 mmol) were added to the reaction mixture and the reaction mixture was stirred at 100°C for the appropriate time as mentioned in Table 2. The progress of the reaction was monitored by TLC using ethyl acetate:petroleum ether (30:70, v/v) as eluent. After completion, the reaction mixture was allowed to cool to room temperature and poured on crushed ice. The separated solid was filtered at pump, dried under vacuum and chromatographed on basic alumina. Elution with a gradient mixture of petroleum ether/ethyl acetate yielded compounds **IIIa-p** as characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

12-(4-Fluorophenyl)-2-(3-((4-methoxyphenyl)amino)propoxy)-9,9-dimethyl-9,10-dihydro-8H-benzo[a]xanthen-11(12H)-one (IIIa)

White solid; Yield = 87%; M.p.=132°C; IR (KBr) ν_{max}, cm^{-1}: 3385, 2927, 1650, 1621, 1374, 1224, ^{1}H NMR (300 MHz, CDCl3): δ 7.68-7.60 (m, 2H, Ar), 7.32-7.25 (m, 2H, Ar), 7.17-7.11 (m, 2H, Ar), 7.02 (d, *J*=8.7 Hz, 1H, Ar), 6.87-6.77 (m, 4H, Ar), 6.62-6.59 (m, 2H, Ar), 5.55-5.51 (m, 1H, CH), 5.28-5.27 (m, 1H, NH, D_2O Exchangeble), 4.15-4.12 (m, 1H, OCH_2), 4.00-3.96 (m, 1H, OCH_2), 3.86-3.69 (m, 3H, OCH_3), 3.32-3.27 (m, 2H, CH_2NH), 2.55 (s, 2H, CH_2CO), 2.33-2.19 (m, 2H, CCH_2), 2.16-1.98 (m, 2H, CH_2CH_2), 1.11 (s, 3H, CH_3), 0.95 (s, 1H, CH_3) ; ^{13}C NMR (300 MHz, $CDCl_3$): 196.84, 163.77, 157.51, 152.29, 148.04, 141.67, 140.37, 132.48, 129.85, 129.75, 128.50, 126.59, 117.35, 116.16, 115.59, 115.02, 114.80, 114.46, 113.75, 103.17, 65.69, 55.61, 53.33, 50.65, 48.86, 42.28, 41.16, 34.21, 32.03, 31.79, 29.56, 29.17, 28.62, 26.85, 26.71,.; HRMS (ESI) $[M+H]^+$ Calc. for $C_{35}H_{34}FNO_4$: 552.2550, found: 552.6635.

9,9-Dimethyl-12-(4-methyl)-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8*H*-benzo [*a*] xanthen-11(12*H*)-one (IIIb)

White solid; Yield =88%; M.p.=120-121°C; IR (KBr) ν_{max}, cm^{-1}: 3411, 2924, 1650, 1619, 1375, 1227, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H, Ar), 7.25-7.21 (m, 3H, Ar), 7.17-7.14 (m, 2H, Ar), 7.01-6.94 (m, 2H, Ar), 6.58-6.56 (m, 2H, Ar), 5.51 (s, 1H, CH), 4.21-4.16 (m, 1H, OCH_2), 4.14-3.97 (m, 1H, OCH_2), 3.70 (s, 1H, NH, D_2O Exchangeble), 3.48-3.30 (m, 2H, NCH_2), 2.56 (s, 2H, CH_2CO), 2.33-2.24 (m, 5H, CCH_2+ CH_3), 2.19 (s, 3H, CH_3), 2.13-2.03 (m, 2H,CCH_2C) 1.11 (s, 3H, CH_3), 0.97 (s, 1H, CH_3) ; ^{13}C NMR (300 MHz, $CDCl_3$): 197.00, 163.72, 157.54, 145.89, 141.79, 129.73, 128.88, 128.31, 114.21, 112.99, 103.32, 65.84, 50.85, 41.36, 32.23, 29.24, 20.95, 20.35; HRMS (ESI) $[M]^+$ Calc. for $C_{36}H_{37}NO_3$: 531.2773, found: 531.5979.

9,9-Dimethyl-12-(3-nitrophenyl)-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8*H*-benzo[*a*] xanthen-11(12*H*)-one (IIIc)

White solid; Yield = 81%; M.p.=172°C; IR (KBr) ν_{max}, cm-1: 3403, 2958, 1650, 1619, 1372, 1223, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H, Ar), 7.9 (d, *J*=7.8Hz, 1H, Ar), 7.73-7.67 (m, 3H, Ar), 7.35-7.29 (m, 1H, Ar), 7.21-7.19 (m, 1H, Ar), 7.12 (s, 1H, Ar), 7.06 (m, 3H, Ar), 6.58 (m, 2H, Ar), 5.66 (s, 1H, CH), 4.23-4.16 (m, 1H, OCH_2), 3.99-3.93 (m, 1H, OCH_2), 3.73 (s, 1H, NH, D_2O Exchangeble), 3.32 (t, *J*=6.4 Hz, 2H, CH_2NH), 2.61 (s, 2H, CH_2CO), 2.36-2.20 (m, 5H, CCH_2+ CH_3), 2.14-2.04 (m, 2H, CH_2CH_2), 1.14 (s, 3H, CH_3), 0.97 (s, 1H, CH_3) ; ^{13}C NMR (300 MHz, $CDCl_3$): 196.86, 164.59, 157.97, 148.30, 148.21, 146.80, 145.94, 134.68, 132.38, 130.19, 129.76, 129.25, 129.11, 126.80, 126.56, 123.37, 121.63, 117.79, 115.10, 114.60, 113.04, 112.98, 102.83, 66.08, 50.75, 41044, 41.38, 35.17, 32.33, 29.27, 29.00, 27.18, 20.37; HRMS (ESI) $[M]^+$ Calc. for $C_{35}H_{34}N_2O_5$: 562.2468, found: 562.1675.

12-(3-Bromophenyl)-9,9-dimethyl-2-(3-(4-methylamino) propoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIId)

White solid; Yield = 88%; M.p.=86°C; IR (KBr) ν_{max}, cm^{-1}: 3406, 2924, 1651, 1622, 1374, 1226, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.61 (m 2H, Ar), 7.52-7.48 (m, 1H, Ar), 7.27-7.25 (m, 1H, Ar), 7.17 (s, 1H, Ar), 7.04-7.01 (m, 2H, Ar), 6.79-6.77 (m, 2H, Ar), 6.62-6.59 (m, 2H, Ar), 5.61 (s, 1H, CH), 5.27 (s, 1H, NH, D_2O Exchangeble), 4.17 (s, 1H, OCH_2), 4.05-3.89 (m, 1H, OCH_2), 3.73 (s, 3H, OCH_3), 3.49-3.30 (m, 2H, CH_2CH_2), 2.56 (s, 2H, CH_2CO), 2.33-2.21 (m, 2H, CCH_2), 2.09 (s, 2H, CH_2CH_2), 1.11 (s, 3H, CH_3), 0.98 (s, 1H, CH_3) ; ^{13}C NMR (300 MHz, $CDCl_3$): 196.88, 164.14, 157.69, 152.22, 148.07, 146.99, 142.11, 132.56, 131.66, 129.97, 129.84, 128.82, 127.25, 126.69, 122.31, 117.68, 115.79, 114.90, 114.50, 114.35, 113.39, 103.39, 66.00, 55.79, 53.46, 50.76, 48.99, 42.29, 41.33, 35.05, 33.84, 29.71, 28.88, 27.20; HRMS (ESI) $[M+H]^+$ Calc. for $C_{35}H_{34}BrNO_4$: 612.1749, found: 612.2366, 614.2370 $[M+H+2]^+$.

12-(4-Bromophenyl)-2-(3-((4-fluorophenyl)amino)propoxy)-9,9-dimethyl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIIe)

White solid; Yield = 83%; M.p.=104°C; IR (KBr) ν_{max}, cm^{-1}: 3468, 2925, 1648, 1620, 1375, 1222, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.68 (m 2H, Ar), 7.28-7.15 (m, 6H, Ar), 7.10-7.03 (m, 1H, Ar), 6.96-6.88 (m, 2H, Ar), 6.71-6.56 (m, 2H, Ar), 5.54 (s, 1H, CH), 4.17-4.14 (m, 1H, OCH_2), 4.02-3.99 (m, 1H, OCH_2), 3.32-3.29 (m, 1H, NH, D_2O Exchangeble), 2.56 (s, 2H, CH_2NH), 2.34-2.22 (m, 2H, CH_2CO), 2.09-2.00 (m, 2H, CCH_2), 1.31-1.28 (m, 2H, CH_2CH_2), 1.12 (s, 3H, CH_3), 0.97 (s, 1H, CH_3) ; ^{13}C NMR (300 MHz, $CDCl_3$): 196.93, 164.06, 157.56, 148.16, 144.45, 143.67, 132.51, 131.24, 130.17, 129.95, 128.69, 126.68, 120.05, 117.47, 115.86, 115.72, 115.49, 114.45, 113.57, 113.49, 103.17, 65.74, 50.72, 41.70, 41.28, 34.55, 32.14, 29.62, 29.22, 28.69, 27.03; HRMS (ESI) $[M+H]^+$ Calc. for $C_{34}H_{31}BrFNO_3$: 600.1550, found: 600.1551, 602.154 $[M+H+2]^+$.

9,9-Dimethyl-12-(naphthalen-2-yl)-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8*H*-benzo [*a*]xanthen-11(12*H*)-one (IIIf)

White solid; Yield = 80%; M.p.=117°C; IR (KBr) ν_{max}, cm^{-1}: 2955, 2868, 1650, 1620, 1372, 1223; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97-7.83 (m, 1H, Ar), 7.78-7.67 (m, 5H, Ar), 7.44-7.23 (m,6H, Ar), 6.98 (s, 2H, Ar), 6.71-6.51 (m, 2H, Ar), 5.73 (s, 1H, CH), 4.17 (s, 1H, OCH_2), 3.94-3.88 (m, 1H, OCH_2), 3.49 (m, 1H, NH, D_2O Exchangeble), 3.25 (s, 2H, CH_2NH), 2.59 (s, 2H, CH_2CO), 2.24 (s, 5H, CCH_2+CCH_3), 2.01-1.87 (m, 2H, CH_2CH_2), 1.12 (s, 3H, CMe), 0.94 (s, 3H, CMe); ^{13}C NMR (300 MHz, $CDCl_3$): 196.99, 163.94, 157.53, 148.21, 145.88, 142.07, 133.25, 132.81, 132.11, 129.85, 129.73, 128.59, 128.03, 127.81, 127.47, 127.23, 126.77, 126.52, 125.86, 125.44, 117.59, 116.49, 114.47, 113.84, 113.00, 103.38, 65.84, 50.87, 41.43, 35.35, 32.23, 29.29, 28.81, 27.21, 26.71, 20.38; HRMS (ESI) $[M]^+$ Calc. for $C_{39}H_{37}NO_3$: 567.2773, found: 567.8737.

12-(4-Methoxyphenyl)-9,9-dimethyl-2-(3-(octylamino)propoxy)-9,10-dihydro-8H-benzo[*a*] xanthen-11(12*H*)-one (IIIg)

Liquid; Yield = 83%; IR (KBr) ν_{max}, cm^{-1}: 2927, 2852, 1651, 1620, 1375, 1225; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.56 (m, 2H, Ar), 7.26-7.20 (m, 3H, Ar), 7.16-7.11 (m, 1H, Ar), 6.98 (dd, *J*=1.95 Hz, *J*=8.85 Hz, 1H, Ar), 6.72-6.68 (m, 2H, Ar), 5.49 (s, 1H, CH), 5.28 (s, 1H, NH, D_2O Exchangeble), 4.11-4.06 (m, 1H, OCH_2), 3.98-3.91 (m, 1H, OCH_2), 3.68-3.62 (m, 3H, OCH_3), 3.31-3.24 (m, 1H, CH_2NH), 2.95-2.90 (m, 1H, CH_2NH), 2.76-2.63 (m, 2H, $NHCH_2$), 2.55 (s, 2H, CH_2CO), 2.33-2.25 (m, 2H, CCH_2), 2.19-1.93 (m, 2H, CH_2CH_2),1.28-1.18 (m, 12H, CH_2aliphatic), 1.11 (s, 3H, CCH_3), 0.97 (s, 3H, CCH_3), 0.88-0.84 (m, 5H, aliphatic CH_2 + CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): 196.91, 163.51, 157.66, 157.22, 147.97, 136.90 132.62, 129.26, 128.21, 126.64, 117.13, 116.72, 113.46, 113.40, 103.27, 65.18, 54.93, 53.33, 50.73, 48.62, 45.81, 41.20, 38.05, 34.05, 32.08, 31.73, 29.35, 29.19, 29.10, 29.05, 27.08, 26.97, 26.92, 26.72, 22.48, 13.95; HRMS (ESI) $[M]^+$ Calc. for $C_{37}H_{47}NO_4$: 569.3505, found: 569.7871.

12-(4-chlorophenyl)-9,9-dimethyl-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8H-benzo[*a*] xanthen-11(12*H*)-one (IIIh)

White solid; Yield = 85%; M.p.=122°C; IR (KBr) ν_{max}, cm^{-1}: 3307, 2955, 2622, 1652, 1638, 1375, 1225, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J*=9.2 Hz, 2H, Ar), 7.14 (d, *J*=9.2 Hz, 1H,

Ar), 7.00-6.97 (m, 2H, Ar), 6.69-6.64 (m, 2H, Ar), 6.55 (d, *J*=6.8 Hz, 2H, Ar), 5.49 (s, 1H, CH), 4.17-4.13 (m, 1H, OCH_2), 4.02-3.98 (m, 1H, OCH_2), 3.66-3.62 (m, 3H, NH, D_2O Exchangeble +CH_2NH), 3.31 (t, *J*=6.8 Hz, 2H, CH_2CO), 2.54 (s, 2H, CCH_2), 2.24-2.20 (m, 3H, CH_3), 2.08-2.05 (m, 2H, CH_2CH_2), 1.10 (s, 3H, CH_3), 0.96 (s, 3H, CH3); ^{13}C NMR (300 MHz, $CDCl_3$): 196.91, 164.02, 157.70, 148.21, 145.87, 143.19, 132.59, 131.92, 129.96, 129.81, 129.77, 128.71, 128.36, 126.72, 126.58, 117.57, 116.02, 114.44, 114.30, 113.68, 113.01, 103.23, 65.84, 50.82, 47.97, 41.37, 34.51, 32.21, 29.27, 28.85, 27.11, 26.86, 20.36; HRMS (ESI) $[M+H]^+$ Calc. for $C_{35}H_{34}ClNO_3$: 552.2305, found: 552.2759, 554.2757 $[M+H+2]^+$.

2-(3-((4-Fluorophenyl)amino)propoxy)-9,9-dimethyl-12-(4-nitrophenyl)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIIi)

White solid; Yield = 83%; M.p.=200°C; IR (KBr)) ν_{max}, cm^{-1}: 3421, 2958, 1650, 1620, 1376, 1225, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J*=7.6 Hz, 2H, Ar), 7.72-7.67 (m, 2H, Ar), 7.48 (d, *J*=8.4 Hz, 2H, Ar), 7.24-7.18 (m, 1H, Ar), 7.04-7.02 (m, 1H, Ar), 6.88-6.84 (m, 2H, Ar), 6.54-6.51 (m, 2H, Ar), 5.65 (s, 1H, CH), 4.15-4.12 (m, 1H, OCH_2), 3.95-3.93 (m, 1H, OCH_2), 3.70 (s, 1H, NH, D_2O Exchangeable), 3.30-3.27 (m, 2H, CH_2NH), 2.57 (s, 2H, CH_2CO), 2.33-2.15 (m, 2H, CCH_2), 2.08-2.05 (m, 2H, CH_2CH_2), 1.12-1.09 (m, 3H, CH_3), 0.97-0.93 (m, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): 196.83, 164.65, 157.81, 156.92, 154.58, 151.83, 148.27, 146.29, 144.44, 132.39, 130.17, 129.29, 129.21, 123.53, 117.61, 115.74, 115.52, 114.53, 113.55, 113.48, 112.83, 102.90, 65.81, 50.68, 41.69, 41.34, 35.09, 32.19, 29.24, 28.81, 27.00; HRMS (ESI) $[M+H]^+$ Calc. for $C_{34}H_{31}FN_2O_5$: 567.2295, found: 567.2296, 569.2335 [M+H+2]+.

12-(4-Methoxyphenyl)-9,9-dimethyl-2-(3-(4-methylamino) propoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIIj)

White solid; Yield = 85%; M.p.=124°C; IR (KBr) ν_{max}, cm^{-1}: 3400, 2949, 1644, 1621, 1375, 1224, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J*=9 Hz, 2H, Ar), 7.26-7.23 (m, 3H, Ar), 7.15 (d, *J*=8.7 Hz, 1H, Ar), 7.00 (d, *J*=7.8 Hz, 3H, Ar), 6.6 (d, *J*=8.4 Hz, 2H, Ar), 6.57 (d, *J*=8.1 Hz, 2H, Ar), 5.51 (s, 1H, CH), 4.20-4.13 (m, 1H, OCH_2), 4.04-3.97 (m, 1H, OCH_2), 3.71-3.67 (m, 4H, NH, D_2O Exchangeble +OCH_3), 3.34-3.30 (m, 2H, CH_2NH), 2.56 (s, 2H, CH_2CO), 2.33-2.20 (m, 5H, CCH_3+CCH_2), 2.10-2.05 (m, 2H, CH_2CH_2), 1.11 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): 197.10, 163.64, 157.78, 157.55, 148.14, 145.92, 137.07, 132.75, 129.84, 129.75, 129.40, 128.34, 126.71, 126.54, 117.47, 116.85, 114.45, 114.27, 113.55, 113.00, 103.40, 65.86, 55.07, 50.89, 41.53, 41.38, 34.19, 32.25, 29.28, 28.87, 27.19, 20.37; HRMS (ESI) $[M]^+$ Calc. for $C_{36}H_{37}NO_4$: 547.2723, found: 547.9974, 548.0637 $[M+H]^+$.

12-(3-Bromophenyl)-9,9-dimethyl-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthene-11(12*H*)-one (IIIk)

White solid; Yield = 82%; M.p.=100°C; IR (KBr)) ν_{max}, cm^{-1}: 3396, 2925, 1642, 1619, 1373, 1224, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 2H, Ar), 7.49 (s, 1H, Ar), 7.26-7.24 (m, 1H, Ar), 7.18-7.14 (m, 3H, Ar), 7.03-6.97 (m, 4H, Ar), 6.57-6.55 (d, *J*=6.3 Hz, 2H, Ar), 5.49 (s, 1H, CH), 4.19-4.15 (m, 1H, OCH_2), 4.00-3.95 (m, 1H, OCH_2), 3.33-3.30 (m, 2H, CH_2NH), 2.57 (s, 2H, CH_2CO), 2.32-2.22 (m, 5H, CCH_3+CCH_2), 2.15-2.06 (m, 1H, NH, D_2O Exchangeble), 1.41-1.40 (m, 1H, CH_2CH_2), 1.28-1.24 (m, 1H, CH_2CH_2), 1.11 (s, 3H, CH_3), 0.97-0.94 (m, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): 196.80, 164.09, 157.69, 148.05, 146.95, 145.88, 132.55, 131.62, 129.92, 129.77, 129.69, 129.43, 128.77, 127.21, 126.67, 126.46, 122.27, 117.65, 115.77, 114.44, 113.38, 112.96, 103.11, 65.98, 50.74, 41.45, 41.32, 35.02, 32.22, 29.18, 28.88, 27.16, 20.34; HRMS (ESI) $[M+H]^+$ Calc. for $C_{35}H_{34}BrNO_3$: 596.1800, found: 596.1822, 598.1797 $[M+H+2]^+$.

2-(3-((4-Methoxyphenyl)amino)propoxy)-12-(4-methyl)-9,10-dihydro-8*H*-benzo [*a*]xanthen-11(12*H*)-one (IIIl)

White solid; Yield = 79%; M.p.=164°C; IR (KBr) ν_{max}, cm^{-1}: 3392, 2948, 1645, 1620, 1374, 1230, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=9 Hz, 2H, Ar), 7.25-7.15 (m, 4H, Ar), 7.01-6.95 (m, 3H, Ar), 6.81-6.78 (m, 2H, Ar), 6.62-6.59 (m, 2H, Ar), 5.55 (s, 1H, CH), 4.21-4.13 (m, 1H, OCH_2), 4.02-3.96 (m, 1H, OCH_2), 3.75 (s, 3H, OCH_3), 3.57 (s, 1H, NH, D_2O Exchangeble), 3.29 (t, *J*=6.6 Hz, 2H, CH_2NH), 2.76-2.65 (m, 2H, CH_2CO), 2.47-2.36 (m, 2H, CCH_2), 2.20 (s, 3H, CH_3), 2.11-1.97 (m, 4H,CH_2CH_2+ CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.13, 165.45, 157.59, 152.15, 148.21, 142.51, 142.14, 135.76, 132.81, 129.84, 128.97, 128.43, 126.75, 117.51, 116.90, 115.62, 114.99, 114.43, 114.18, 103.45, 65.95, 55.87, 42.22, 37.07, 34.65, 28.99, 27.75, 21.00, 20.33; HRMS (ESI) $[M]^+$ Calc. for $C_{34}H_{33}NO_4$: 519.2410, found: 519.2202.

12-(4-Nitrophenyl)-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8H-benzo [*a*]xanthen-11(12*H*)-one (IIIm)

White solid; Yield = 75%; M.p.=187°C; IR (KBr) ν_{max}, cm^{-1}: 3408, 2924, 1638, 1620, 1374, 1229, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 2H, Ar), 7.72 (s, 2H, Ar), 7.51 (s, 2H, Ar), 7.26-7.22 (m, 1H, Ar), 7.03 (s, 4H, Ar), 6.57 (s, 2H, Ar), 5.69 (s, 1H, CH), 4.14 (s, 1H, OCH_2), 3.95 (s, 1H, OCH_2), 3.69 (s, 1H, NH, D_2O Exchangeble), 3.43-3.33 (m, 2H, CH_2NH), 2.74 (s, 2H, CH_2CO), 2.43 (s, 2H, CCH_2), 2.24 (s, 3H, CH_3), 2.09 (s, 4H, CH_2CH_2+ CH_2 CH2); ^{13}C NMR (300 MHz, $CDCl_3$): 196.85, 166.32, 158.09, 152.10, 148.57, 146.37, 130.15, 129.78, 129.39, 129.24, 123.62, 117.64, 115.03, 114.42, 114.18, 112.96, 102.96, 65.89, 41.40, 36.90, 35.06, 28.89, 27.75, 20.3.5, 20.20; HRMS (ESI) $[M]^+$ Calc. for $C_{33}H_{30}N_2O_5$: 534.2155, found: 534.8673.

12-(4-Methoxyphenyl)-2-(3-(4-methylamino)propoxy)-9,10-dihydro-8H-benzo [*a*]xanthen-11(12*H*)-one (IIIn)

White solid; Yield = 83%; M.p.=165°C; IR (KBr) ν_{max}, cm^{-1}: 3406, 2940, 1643, 1618, 1376, 1227, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J*=9 Hz, 2H, Ar), 7.26-7.23 (m, 2H, Ar), 7.19-7.15 (m, 2H, Ar), 6.99 (d, *J*=8.1 Hz, 2H, Ar), 6.69 (d, *J*=8.4 Hz, 2H, Ar), 6.57 (d, *J*=8.4 Hz, 2H, Ar), 5.54 (s, 1H, CH), 4.19-4.13 (m, 1H, OCH_2), 4.02-3.95 (m, 1H, OCH_2), 3.68 (s, 4H, NH, D_2O Exchangeble +OCH_3), 3.32 (t, *J*=6.6 Hz, 2H, CH_2NH), 2.76-2.65 (m, 2H, CH_2CO), 2.48-2.37 (m, 2H, CCH_2), 2.24 (s, 3H, CH_3), 2.11-1.98 (m, 4H,CH_2CH_2+ CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.23, 165.36, 157.88, 157.57, 148.21, 145.97, 137.40, 132.79, 126.86, 129.78, 129.51, 128.37,

126.75, 126.57, 117.49, 116.89, 115.63, 114.42, 113.64, 113.04, 103.52, 65.91, 55.11, 41.57, 37.08, 34.17, 28.92, 27.74, 20.38, 20.35, ; HRMS (ESI) $[M]^+$ Calc. for $C_{34}H_{33}NO_4$: 519.2410, found: 519.3685.

12-(4-Bromophenyl)-2-(3-((4-methoxyphenyl)amino)propoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIIo)

White solid; Yield = 77%; M.p.=118°C; IR (KBr) ν_{max}, cm^{-1}: 3345, 2934, 1650, 1620, 1372, 1224, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (dd, *J*=3.3 Hz, *J*=8.7 Hz, 2H, Ar), 7.29-7.26 (m, 3H, Ar), 7.22-7.16 (m, 3H, Ar), 7.10 (s, 1H, Ar), 7.03 (dd, *J*=1.95 Hz, *J*=8.85Hz, 1H, Ar), 6.81-6.79 (m, 2H, Ar), 6.63 (m, 2H, Ar), 5.55 (s, 1H, CH), 4.19-4.12 (m, 1H, OCH_2), 4.01-3.94 (m, 1H, OCH_2), 3.75 (s, 3H, OCH_3), 3.56 (s, 1H, NH, D_2O Exchangeble), 3.30 (t, *J*=6.6 Hz, 2H, CH_2NH), 2.73-2.66 (m, 2H, CH_2CO), 2.45-2.38 (m, 2H, CH_2CH_2), 2.11-1.96 (m, 4H, CH_2CH_2+ CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.09, 165.75, 157.71, 152.16, 148.27, 144.02, 142.44, 132.60, 131.36, 130.32, 129.99, 128.77, 126.76, 120.15, 117.60, 115.96, 115.00, 114.41, 114.18, 103.28, 65.91, 55.87, 42.09, 37.01, 34.58, 28.92, 27.75, 20.29; HRMS (ESI) $[M+H]^+$ Calc. for $C_{33}H_{30}BrNO_4$: 584.1436, found: 584.1973, 586.1968 $[M+H+2]^+$.

12-(4-Fluorophenyl)-2-(3-((4-methoxyphenyl)amino)propoxy)-9,10-dihydro-8*H*-benzo[*a*]xanthen-11(12*H*)-one (IIIp)

White solid; Yield = 78%; M.p.=153°C; IR (KBr) ν_{max}, cm^{-1}: 3382, 2947, 1645, 1620, 1374, 1227, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H, Ar), 7.31-7.26 (m, 2H, Ar), 7.19-7.12 (m, 2H, Ar), 7.03 (d, *J*=9 Hz, 1H, Ar), 6.87-6.78 (m, 4H, Ar), 6.62-6.59 (m, 2H, Ar), 5.58 (s, 1H, CH), 4.19-4.12 (m, 1H, OCH_2), 3.99-3.93 (m, 1H, OCH_2), 3.75 (s, 3H, OCH_3), 3.56 (s, 1H, NH, D_2O Exchangeble), 3.32-3.28 (m, 2H, CH_2NH), 2.77-2.66 (m, 2H, CH_2CO), 2.49-2.32 (m, 2H, CH_2CH_2), 2.09-1.97 (m, 4H, CH_2CH_2+ CH_2CH_2); ^{13}C NMR (300 MHz, $CDCl_3$): 197.19, 165.62, 159.59, 157.63, 152.11, 148.22, 147.58, 142.40, 140.77, 132.61, 130.04, 129.93, 128.63, 126.73, 117.52, 116.33, 115.19, 114.94, 114.40, 114.13, 103.31, 65.89, 55.82, 42.10, 37.01, 34.27, 28.91, 27.71, 20.28; HRMS (ESI) $[M+H]^+$ Calc. for $C_{33}H_{30}FNO_4$: 524.2237, found: 524.0953.

Antimicrobial Assay

Test microorganisms

Total four bacterial strains were selected on the basis of their clinical importance in causing diseases in humans. Two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 121); two Gram-negative bacteria (*Escherichia coli* MTCC 1652 and *Pseudomonas aeruginosa* MTCC 741) were screened for evaluation of antibacterial activity of the 2-(3-aryl/alkylaminopropoxy)-12-aryl xanthene derivatives. All the microbial cultures were procured from Microbial Type Culture Collection (MTCC), IMTECH, Chandigarh. The bacteria were subcultured on Nutrient agar.

Antibacterial activity (bacteria and yeasts)

The antibacterial activity of 2-(3- aryl/alkylaminopropoxy)-12-aryl xanthene derivatives was evaluated by the agar well diffusion method. All the microbial cultures were adjusted to 0.5 McFarland standard, which is visually comparable to a microbial suspension of approximately 1.5 ×108 cfu/mL. 20 mL of agar medium was poured into each Petri plate and plates were swabbed with 100 µL inocula of the test microorganisms and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µL of 4.0 mg/mL of each compound reconstituted in the dimethyl sulphoxide (DMSO). All the plates were incubated at 37°C for 24 h. Antibacterial activity of each 2-(3- aryl/alkyl amino propoxy)-12-aryl xanthene derivatives was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (Hi Antibiotic zone scale). DMSO was used as a negative control whereas ciprofloxacin was used as positive control. This procedure was performed in three replicate plates for each organism.[29]

Conclusion

In conclusion, we have synthesized a series of novel biologically important 2-(3-alkyl/arylaminopropoxy)-12-aryl-9,10-dihydro-8*H*-benzo[*a*]xanthen-11-one derivatives by the reaction of 2-hydroxy-12-aryl xanthene derivatives with 1-bromo-3-chloropropane in presence of K_2CO_3 in dry acetone under reflux followed by reaction with aryl/alkyl amines in presence of KI in dry DMF at 100°C in good yields. The synthesized 2-(3- alkyl/arylaminopropoxy)-xanthene derivatives were well characterized and screened for their antibacterial and antifungal activities, some of them have shown good antimicrobial and antifungal activities.

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