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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and in vitro antibacterial screening of some novel 3-pentyloxy-1-hydroxyxanthone derivatives

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Abstract A series of 3-pentyloxy-1-hydroxyxanthone derivatives were synthesized by four-step reactions: first cyclocondensation between salicylic acid and phloroglucinol in the presence of Eaton's reagents, then alkylation with 1,5-dibromopentane, followed by nucleophilic substitution by different nucleophiles to obtain final compounds. Molecular structures of the synthesized compounds were elucidated by FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, and elemental analysis. The in vitro antibacterial activity was evaluated by MIC determination using broth dilution method against representative three Gram-positive and three Gram-negative bacterial strains with reference to ofloxacin. All the synthesized compounds showed antibacterial activity; besides the compounds **7f** and **7g** showed better Gram-positive and Gram-negative antibacterial activities.

Keywords Xanthone · Antibacterial · Zone of inhibition · Phloroglucinol

Introduction

Currently, problems relating to multidrug-resistant microorganisms have reached an alarming level all over the world. Resistance to a number of antimicrobial agents (β-lactam antibiotics, macrolides, quinolones, and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly major global problem. The continual emergence of bacterial resistance to most classes of antibiotics is a cause for great concern and creates a pressing need for newer antibacterial agents (Francis *et al.*, 2004; Kruszewska *et al.*, 2004). While searching for compounds with potential antibacterial activity, we directed our attention to the xanthone derivatives, which show several beneficial heterogenous and varied pharmacological properties: for example, analeptic (Quintas *et al.*, 2003), anticonvulsant (Marona *et al.*, 2008), antilipidemic (Gion *et al.*, 1982), diuretic (Sato *et al.*, 1990), antitumor (Castanheiro *et al.*, 2007; Varache-Lembege *et al.*, 2008), protein kinase C inhibitors (Saraiva *et al.*, 2003), antimycotics (Moreau *et al.*, 2002), antimalarial (Dodean *et al.*, 2008), anti-inflammatory, antihypertensive (Wang *et al.*, 2002), α-glucosidase inhibitors (Liu *et al.*, 2007) and antioxidant (Lee *et al.*, 2005). Fukai et al. (2005) isolated some isoprenoid-substituted xanthones from *Cudrania cochinchinensis* which had antimicrobial activity against vancomycin-resistant *enterococci*.

As naturally occurring xanthones showed good antibacterial activity with low side effect, we consider the xanthone scaffold for discovery of newer antibiotics. It was found that 3,6-bis-ω-(*N*,*N*-diethylaminoalkoxy) xanthones have good antimalarial activity (Kelly *et al.*, 2002). In this article, we report on the synthesis, structural characterization, and preliminary evaluation of the antibacterial properties of a number of novel 3-pentyloxy-1-hydroxyxanthone derivatives.

Chemistry

As we were interested in analyzing the relationship between structure and antibacterial activity, we synthesized appropriate substituted 3-pentyloxy-1-hydroxyxanthones. The general synthetic route used for the target xanthones is illustrated in Scheme 1.

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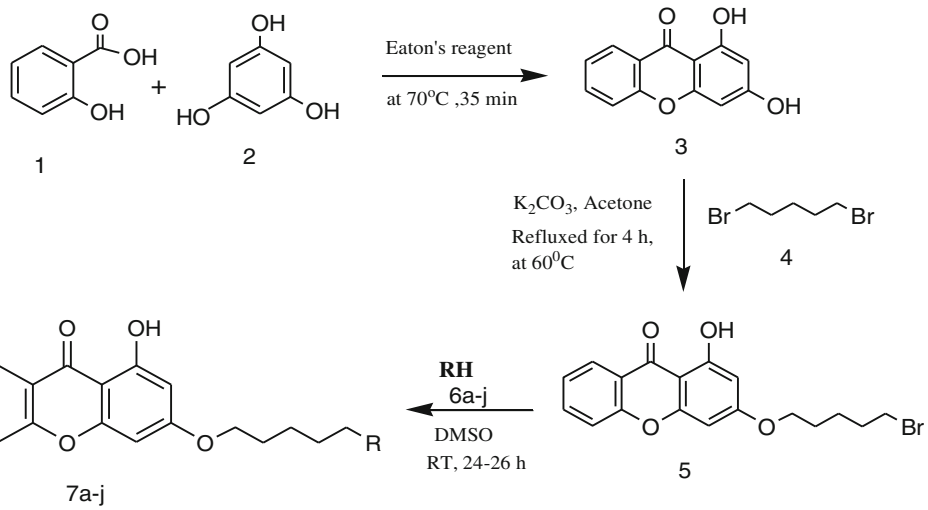
Scheme 1 Schematic representation of the synthesis of 3-pentyloxy-1-hydroxyxanthone derivatives



The procedure for preparing hydroxylated xanthones is the cyclization reaction between phloroglucinols and appropriate substituted salicylic acids, in the presence of a mixture of phosphorus pentoxide–methanesulfonic acid (Eaton's reagent) as catalyst which gives higher yield (Eaton *et al.*, 1973). According to this method, 1,3-dihydroxyxanthone (**3**) was obtained by cyclization of salicylic acid (**1**) and phloroglucinol (**2**) in the presence of Eaton's reagent. Then, 3-hydroxyl group of compound **3** was alkylated by 1,3-dibromopentane (**4**) to produce 3-(5-bromopentyloxy)-1-hydroxyxanthone (**5**) in the presence of potassium carbonate. Due to hydrogen bond formation between oxygen of 9-keto and 1-hydroxyl groups, the 1-hydroxyl group could not be alkylated. Finally, target compounds (**7a–j**) were prepared by means of nucleophilic substitution of bromine atom from compound **4** using various nucleophilic reagents RH (**6a–j**).

Pharmacology

Antibacterial activity

The in vitro antibacterial potency of all the synthesized compounds were evaluated against selected three representative Gram-positive organisms, viz., *Bacillus subtilis* (ATCC 6633, NCIM 2063), *Bacillus cereus* (ATCC 10876, NCIM 2156), and *Staphylococcus aureus* (ATCC 6538, NCIM 2079); and three Gram-negative organisms, viz., *Escherichia coli* (ATCC 8739, NCIM 2065), *Proteus mirabilis* (NCIM 2241), and *Pseudomonas aeruginosa* (ATCC 19429, NCIM 2036) along with ofloxacin as reference antibiotic. The microbial strains used for antibacterial study were procured from National Collection of Industrial Micro-organisms (NCIM), Pune, India.

Results and discussion

All the spectral data obtained are exactly according to the assumed structure of synthesized compounds. The elemental analysis results were within ±0.4 % of the theoretical values, i.e., synthesized compounds were fully pure. The antibacterial activities of all the synthesized compounds were observed, and all of these show antibacterial activity in comparison with ofloxacin. Besides these, three compounds (**7b**, **7d**, and **7e**) displayed low-to-moderate activity against only Gram-positive bacteria, while three compounds (**7a**, **7c**, and **7h**) showed good susceptibility against only Gram-negative bacterial strain, and other four compounds (**7f**, **7g**, **7i**, and **7j**) showed good activity against both Gram-positive and Gram-negative bacteria strain. Compounds **3** and **5** showed negligible or no antibacterial activity against used microorganisms. The zones of inhibition of 3-pentyloxy-1-hydroxyxanthone derivatives against representative bacterial strains are represented in Table 2. The minimum inhibitory concentration value of synthesized compounds was found to be in the range of 4–32 μg ml^{-1}, and these are given in Table 3. Most of the newly synthesized compounds showed significant antibacterial activity against *B. subtilis*, *S. aureus*, and *P. aeruginosa*. The compound **7f** showed broad spectrum activity, while compound **7d** showed activity against only *B. subtilis*. Two compounds **7f** and **7g** showed better minimum inhibitory concentration (MIC) value in comparison with others which have an introduction of electron-withdrawing group or groups containing primary aromatic amine.

Conclusion

In conclusion, the series of novel 3-pentyloxy-1-hydroxyxanthones were synthesized and evaluated for in vitro

antibacterial activity. The simplicity of preparation and better yield in significantly short reaction time can potentially make this procedure as a useful and attractive alternative for the synthesis of newer antibacterial compounds. The compounds **7f** and **7g** showed significant activity in comparison with ofloxacin. Therefore, we can conclude that an introduction of electron-withdrawing group or groups containing primary aromatic amine in the 3-pentyloxy-1-hydroxyxanthone at 5′ position significantly increases the antibacterial activity against both Gram-positive and Gram-negative bacteria strains. We can consider these two compounds (**7f** and **7g)** for further investigation as newer antibiotics suitable for bacterial resistance. The 3-(ω-substituted alkoxy)xanthones are considered as a newer series of antibiotics by changing alkoxy chain instead of pentyloxy and substitution attached.

Experimental protocol

All the reagents were A.R grade and used without further purification. Melting points were determined in open capillaries using Veego melting point apparatus. The FT-IR spectra were recorded using KBr pellets on SHIMADZU-FT-IR spectrophotometer. The ^{1}H NMR spectra were recorded on Bruker Avance–II (400 MHz) spectrometer, and ^{13}C NMR on Bruker Avance–II (100 MHz) spectrometer was performed using dimethylsulfoxide (DMSO)-d_6 and D_2O as solvent with TMSi as an internal standard. The mass spectra were recorded on Water ZQ-4000 mass spectrometer. Elemental analysis was performed using a Perkin Elmer 2400 Series II CHN Analyzer.

Synthesis of 1,3-dihydroxyxanthone (**3**)

Phosphorous pentoxide was dissolved in methane sulfonic acid in the ratio 1:10 to produce Eaton's reagent (Eaton *et al.*, 1973). Dehydrated phloroglucinol (60 mmol) and salicylic acid (60 mmol) were mixed, and previously prepared 100 ml of Eaton's reagent was added slowly to it. Then, the mixture was kept stirring at about 70 °C for 35 min. After cooling the mixture to room temperature, the reaction mixture was poured into crushed ice and stirred for about 2.5 h. The resulting solid was collected, washed with distilled water, and recrystallized from the afforded compound **3** as reddish-brown color solid, yield 76.45 %, m.p. 120–122 °C, IR (KBr, v cm^{-1}): 3585.79 (O–$H_{stretch}$) 2951.19 (C–$H_{stretch}$ Ar.), 1660.77 (C=$O_{stretch}$), 1563.75 and 1485.24 (C=$C_{stretch}$ Ar. ring), 1442.80 (O–H_{bend}), 1182.40 (C–$O_{stretch}$ 6-member cyclic ether), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.66 (dd, 1H arom., J = 7.5, 2 Hz), 7.41 (dd, 1H arom., J = 7.5, 2 Hz), 7.1 (dd, 1H arom., J = 7.5, 7.5 Hz), 7.02 (dd, 1H arom., J = 7.5, 7.5 Hz), 6.21 (d, 1H arom., J = 2 Hz), 6.13 (d, 1H arom., J = 2 Hz), 5.12 (s, 1H, OH), 5.06 (s, 1H, OH), ^{13}C NMR (100 MHz, DMSO-d_6): 182.25 (CO), 163.3, 163.28, 158.5, 155.7 (4 × quat. arom. C), 132.21, 130.03, 121.6 (3 × arom. CH), 121.02 (quat. arom. C), 117.2 (arom. CH), 102.62 (quat. arom. C), 96.4, 97.52 (2 × arom. CH), mass (*m/e*): 228.2 [M^+], calc. for: $C_{13}H_8NO_4$: C, 68.42 and H, 3.53 %, found: C, 68.47 and H, 3.54 %.

Synthesis of 3-(5-bromopentyloxy)-1-hydroxyxanthone (**5**)

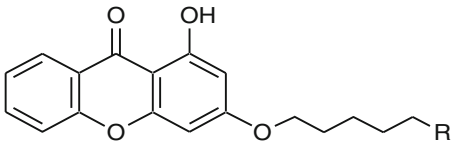
A mixture of 1,3-dihydroxyxanthone (0.2 mmol) and 1,3-dibromopentane (0.2 mmol) was dissolved in acetone, and potassium carbonate (0.25 mmol) was added to neutralize hydrobromic acid. The mixture was refluxed under stirring at 60 °C for 4 h. After cooling, the mixture was filtered and the filtrate was concentrated to obtain crude product. By flash chromatography, pure compound **4** was obtained as light yellow color solid, yield 72.39 %, m.p. 160–164 °C; IR (KBr, v cm^{-1}): 3535.64 (O–$H_{stretch}$), 2729.37 (C–$H_{stretch}$ alkyl), 1618.33 (C=$O_{stretch}$), 1553.28 and 1488.36 (C=$C_{stretch}$ Ar. ring), 1489.10 (O–H_{bend}), 1182.21 (C–$O_{stretch}$ 6-member cyclic ether), 1008.80 (C–$O_{stretch}$ alkyl ether), 663.53 (C–$Br_{stretch}$), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.63 (dd, 1H arom., J = 8, 1.5 Hz), 7.4 (dd, 1H arom., J = 8, 1.5 Hz), 7.08 (dd, 1H arom., J = 8, 1.5 Hz), 7.01 (dd, 1H arom., J = 8, 1.5 Hz), 6.14 (dd, 1H arom., J = 8, 1.5 Hz), 6.06 (s, 1H arom.), 5.11 (s, 1H, OH), 3.49 (*t*, 2H, J = 6.7 Hz, CH_2 near O), 3.31 (*t*, 2H, J = 6.7 Hz, CH_2 near N), 1.8 (m, 2H, J = 6.3 Hz, CH_2), 1.71 (m, 2H, J = 6.3 Hz, CH_2), 1.29 (m, 2H, J = 6.3 Hz, CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.3 (CO), 162.53, 162.36, 157.71, 155.69 (4 × quat. arom. C), 132.21, 130.06, 121.62 (3 × arom. CH), 121.03 (quat. arom. C), 117.21 (arom. CH), 101.63 (quat. arom. C), 96.63, 95.03 (2 × arom. CH), 68.94 (CH_2 nearest to O), 33.7, 32.72, 28.8, 24.38 (4 × CH_2), mass (*m/e*): 376.04 [M^+], 378.03 [$(M+2)^+$] (97.3 %), calc. for: $C_{18}H_{17}BrO_4$: C, 53.31 and H, 4.54 %; found: C, 53.35 and H, 4.53 %.

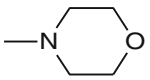
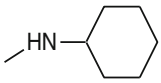
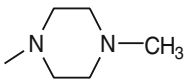
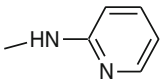
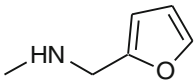
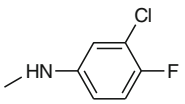
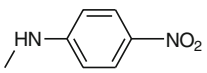
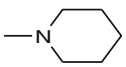
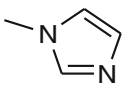
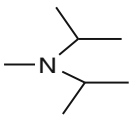
Synthesis of 3-(5-substituted pentyloxy)-1-hydroxyxanthone (**7a–j**)

The 3-(5-bromopentyloxy)-1-hydroxyxanthone (10 mmol) and various selected nucleophilic reagents (10 mmol) were dissolved in 20 ml of DMSO and stirred at room temperature for 24–26 h. At the end of the reaction, the mixture was poured into 50 ml of water and extracted with 50 ml of ether three times. The mixed extracts were condensed and collected as purified product using column chromatography over silica gel.

All the synthesized compounds (Table 1) were characterized by spectroscopic data as FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, and elemental analysis.

Table 1 Structure and physical data of the synthesized compounds



Compound	–R	M.p.	Mol. formula	Mol. wt.	Yield (%)
7a		236–238	$C_{22}H_{25}NO_5$	383.44	69.78
7b		224–226	$C_{24}H_{29}NO_4$	395.49	64.35
7c		146–148	$C_{23}H_{28}N_2O_4$	396.48	74.67
7d		152–154	$C_{23}H_{22}N_2O_4$	390.43	78.56
7e		178–180	$C_{23}H_{23}NO_5$	393.43	71.23
7f		212–214	$C_{24}H_{21}ClFNO_4$	441.88	77.47
7g		164–166	$C_{24}H_{22}N_2O_6$	434.44	79.48
7h		219–221	$C_{23}H_{27}NO_4$	381.46	78.36
7i		167–169	$C_{21}H_{20}N_2O_4$	364.39	75.67
7j		143–145	$C_{24}H_{31}NO_4$	397.51	73.84

*1-Hydroxy-3-(5-morpholinopentyloxy)-9H-xanthen-9-one (**7a**)*

The compound **5** with morpholine (**6a**) was yielded as a brown solid, IR ((KBr, ν_{max} cm^{-1}): 3512.19 (O–$H_{stretch}$), 3094.0 (C–$H_{stretch}$ Ar), 2955.04 (C–$H_{stretch}$), 1666.56 (C=$O_{stretch}$), 1599.04 and 1553.28 (C=$C_{stretch}$ Ar), 1404.22 (C–$N_{stretch}$), 1128.36 (C–$O_{stretch}$ ether), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, 1H arom., $J = 6.8$ Hz, H8), 7.46 (*t*, 1H arom., $J = 6.8$ Hz, H6), 7.12 (*t*, 1H arom., $J = 6.8$ Hz, H7), 7.01 (d, 1H arom., $J = 6.8$ Hz, H5), 6.1 (s, 1H arom., H4), 6.05 (s, 1H arom., H2), 5.53 (s, 1H, OH), 3.96 (*t*, 2H, $J = 5.7$ Hz, CH_2 near O), 3.67 (2 × *t*, 2H, $J = 12.5$ Hz, cyclic CH_2 near O), 2.4 (2 × *t*, 2H,

$J = 12.5$ Hz, CH_2 near N of morpholine), 2.34 (*t*, 2H, $J = 5.7$ Hz, CH_2 near N), 1.72 (m, 2H, $J = 5.9$ Hz, CH_2), 1.39 (m, 2H, $J = 5.9$ Hz, CH_2), 1.29 (m, 2H, $J = 5.9$ Hz, CH_2), ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.3 (CO), 162.61, 162.36, 157.81, 155.86 (4 × quat. arom. C), 132.23, 130.06, 121.64 (3 × arom. CH), 121.02 (quat. arom. C), 117.23 (arom. CH), 101.61 (quat. arom. C), 96.02, 95.01 (2 × arom. CH), 68.97, 66.82 (3 × CH_2 nearest to O), 54.42, 53.71 (3 × CH_2 nearest to N), 29.41, 28.5, 23.72 (3 × CH_2), mass (*m/e*): 383.2 [M^+], calc. for: $C_{22}H_{25}NO_5$: C, 68.91, H, 6.57, N, 3.65 %; found: C, 68.87, H, 6.53, N, 3.62 %.

*3-[5-(Cyclohexylamino) pentyloxy]-1-hydroxy-9H-xanthen-9-one (**7b**)*

The compound **5** with cyclohexylamine (**6b**) was yielded as a light brown solid, FT-IR (KBr, ν_{max} cm^{-1}): 34412.19 ($O–H_{stretch}$), 3092.42 ($C–H_{stretch}$ Ar), 3236.66 ($N–H_{stretch}$ NH), 2955.04 ($C–H_{stretch}$ alkyl), 1666.55 ($C{=}O_{stretch}$), 1504.34 and 1404.22 ($C{=}C_{stretch}$ Ar. ring), 1128.36 ($C–O_{stretch}$ ether), H^1 NMR (400 MHz, DMSO-d_6): δ 7.76 (d, 1H arom., $J = 7.43$ Hz, H), 7.43 (*t*, 1H arom., $J = 7.24$ Hz, H6), 7.1 (*t*, 1H, $J = 7.24$ Hz, H7), 7.01 (d, 1H arom., $J = 8.0$ Hz, H5), 6.63 (s, 1H arom., H4), 6.51 (s, 1H arom., H2), 5.36 (s, 1H, OH), 4.32 (*t*, 2H, $J = 2.17$ Hz, CH_2 near O), 2.57 (m, 1H, $J = 2.4$ Hz, CH near N), 2.4 (*t*, 2H, $J = 2.14$ Hz, CH_2 near N), 2.3 (q, 1H, $J = 2.1$ Hz, NH), 1.81 (m, 2H, $J = 6.9$ Hz, CH_2), 1.64 (m, 2H, $J = 6.9$ Hz, CH_2), 1.57 (m, 2H, $J = 6.9$ Hz, CH_2), 1.46–1.26 (m, 2H, $J = 6.9$ Hz, CH_2), C^{13} NMR (100 MHz, DMSO-d_6): δ 182.2 (CO), 162.5, 162.31, 157.7, 155.69 (4 × quat. arom. C), 132.2, 129.98, 121.6 (3 × arom. CH), 121.02 (quat. arom. C), 117.24 (arom. CH), 101.6 (quat. arom. C), 96.02, 94.93 (2 × arom. CH), 68.89 (CH_2 nearest to O), 56.3, 47.7 (2 × CH_2 nearest to N), 34.31, 30.92, 29.43, 27.98, 23.4, 23.2 (8 × CH_2), mass (*m/e*): 395.7 [M^+], calc. for $C_{24}H_{29}NO_4$: C, 72.89, H, 7.39, N, 3.54 %, found: C, 72.91, H, 7.36, N, 3.51 %.

*1-Hydroxy-3-[5-(4-methylpiperazin-1-yl)pentyloxy]-9H-xanthen-9-one (**7c**)*

The compound **5** with methyl piperazine (**6c**) was yielded as a brown solid, IR (KBr, ν_{max} cm^{-1}): 3425.35 ($O–H_{stretch}$), 3094.32 ($C–H_{stretch}$ Ar), 2906.73 ($C–H_{stretch}$ alkyl), 1678.32 ($C{=}O_{stretch}$), 1583.56 and 1465.90 ($C{=}C_{stretch}$ Ar. ring), 1354.21 ($C–N_{stretch}$), 1128.36 ($C–O_{stretch}$ ether) H^1 NMR (400 MHz, D_2O): δ 7.74 (d, 1H arom., $J = 6.49$ Hz, H8), 7.39 (*t*, 1H arom., $J = 7.64$ Hz, H6), 7.12 (*t*, 1H arom., $J = 12.8$ Hz, H7), 6.92 (d, 1H arom., $J = 12.8$ Hz, H5), 6.09 (s, 1H arom., H4), 6.02 (s, 1H arom., H2), 5.24 (s, 1H, OH), 3.94 (*t*, 2H, $J = 7.21$ Hz, CH_2 near of O), 2.46 (4 × *t*, 2H, $J = 14.4$ Hz, CH_2 of piperazine), 2.35 (*t*, 2H, $J = 7.21$ Hz, CH_2 near N), 2.27 (s, 3H, CH_3), 1.71 (m, 2H, $J = 7.28$ Hz, CH_2), 1.44 (m, 2H, $J = 7.28$ Hz, CH_2), 1.29 (m, 2H, $J = 7.28$ Hz, CH_2), C^{13} NMR (100 MHz, D_2O): δ 182.29 (CO), 162.52, 162.31, 157.69, 155.7 (4 × quat. arom. C), 132.19, 130.02, 121.61 (3 × arom. CH), 121.58 (quat. arom. C), 117.21 (arom. CH), 101.6 (quat. arom. C), 96.02, 94.91 (2 × arom. CH), 68.9 (CH_2 near of O), 55.72, 55.21, 54.13 (5 × CH_2 near of N), 43.11 (CH_3), 29.41, 28.4, 23.72 (3 × CH_2), mass (*m/e*): 396.6 [M^+]. Calc. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07 %; found: C, 69.71; H, 7.15; N, 7.05 %.

*1-Hydroxy-3-[5-(pyridin-2-ylamino)-pentyloxy]-9H-xanthen-9-one (**7d**)*

\The compound **5** with 2-amino pyridine (**6d**) was yielded as a gray solid, IR (KBr, ν_{max} cm^{-1}): 3512.53 ($O–H_{stretch}$), 3264.89 ($N–H_{stretch}$), 3096.34 ($C–H_{stretch}$ Ar), 1674.21 ($C{=}O_{stretch}$), 1591.27 ($N–H_{bend}$), 1545.32 and 1489.05 ($C{=}C_{stretch}$ Ar. ring), 1392.61 ($O–H_{bend}$), 1321.24 ($C–N_{stretch}$), 1128.09 ($C–O_{stretch}$ ether), H^1 NMR (400 MHz, DMSO-d_6): δ 8.11 (d, 1H arom., $J = 5.36$ Hz), 7.66 (d, 1H arom., $J = 5.36$ Hz), 7.44 (*t*, 1H arom., $J = 5.36$ Hz), 7.4 (*t*, 1H arom., $J = 5.36$ Hz), 7.12 (*t*, 1H arom., $J = 5.36$ Hz), 7.04 (d, 1H arom., $J = 5.36$ Hz), 6.7 (d, 1H arom., $J = 5.36$ Hz), 6.6 (*t*, 1H arom., $J = 5.36$ Hz), 6.1 (s, 1H arom.), 6.06 (s, 1H arom.), 5. 53 (s, 1H, OH), 4.06 (*t*, 1H, $J = 2.24$ Hz, NH), 3.94 (*t*, 2H, $J = 4.8$ Hz, CH_2 near O), 3.06 (q, 2H, $J = 6.8$ Hz, CH_2 near N), 1.72 (m, 2H, $J = 6.8$ Hz, CH_2), 1.52 (m, 2H, $J = 6.8$ Hz, CH_2), 1.29 (m, 2H, $J = 6.8$ Hz, CH_2), C^{13} NMR (100 MHz, DMSO-d_6): δ 182.21 (CO), 162.53, 162.3, 158.62, 157.71, 157.7 (5 × quat. arom. C), 148.23 138.3, 132.2, 130.02, 121.6 (5 × arom. CH), 121.01 (quat. arom. C), 117.2, 113.32, 109.9 (3 × arom. CH), 101.61 (quat. arom. C), 96.01, 94.92 (2 × arom. CH), 68.92 (CH_2 near of O), 45.12 (CH_2 near of N), 30.2, 29.4, 23.41 (3 × CH_2), mass (*m/e*): 389.5 [M^+], calc. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17 %; found: C, 70.73; H, 5.70; N, 7.14 %.

*3-[5-[(Furan-2-ylmethyl) amino] pentyloxy]-1-hydroxy-9H-xanthen-9-one (**7e**)*

The compound **5** with furan-2-ylmethyl amine (**6e**) was yielded as a brown solid, IR(KBr, ν_{max} cm^{-1}): 3489.43 ($O–H_{stretch}$), 3249.46 ($N–H_{stretch}$), 3093.57 ($C–H_{stretch}$, Ar), 2904.80 ($C–H_{stretch}$, alkyl), 1651.07 ($C{=}O_{stretch}$), 1593.20 ($N–H_{bend}$), 1552.14 and 1487.12 ($C{=}C_{stretch}$, Ar. ring), 1409.96 ($O–H_{bend}$), 1373.32 ($C–N_{stretch}$), 1127.83 ($C–O_{stretch}$, ether); H^1 NMR (400 MHz, D_2O): δ 7.66 (d, 1H arom., $J = 8.02$ Hz), 7.52 (*t*, 1H arom., $J = 8.02$ Hz), 7.29 (d, 1H arom., $J = 8.02$ Hz), 7.09 (*t*, 1H arom., $J = 8.02$ Hz), 7.0 (d, 1H arom, $J = 8.02$ Hz), 6.28 (*t*, 1H

arom., $J = 8.02$ Hz), 6.1 (s, 1H arom.), 6.06 (s, 1H arom.), 6.02 (d, 1H arom.), 4.8 (s, 1H, OH), 3.94 (*t*, 2H, $J = 6.8$ Hz, CH_2 near of O), 3.66 (d, 2H, $J = 6.8$ Hz, CH2 between N and furan), 2.55 (q, 2H, $J = 6.8$ Hz, CH_2 near of N), 2.13 (m, 1H, $J = 6.8$ Hz, NH), 1.71 (m, 2H, $J = 6.8$ Hz, CH_2), 1.41 (m, 2H, $J = 6.8$ Hz, CH_2), 1.28 (m, 2H, $J = 6.8$ Hz, CH_2), C^{13} NMR (100 MHz, D_2O): δ 182.21 (CO), 162.51, 162.32, 157.72, 155.7, 148.8 (5 × quat. arom. C), 142.11, 132.21, 130.02, 121.63 (4 × arom. CH), 121.6 (quat. arom. C), 117.21, 110.6, 106.7 (3 × arom. CH), 101.61 (quat. arom. C), 96.02, 94.9 (2 × arom. CH), 68.9 (CH_2 near of O), 50.21, 47.11 (CH_2 near of N), 30.01, 29.4, 23.41 (3 × CH_2), mass (*m*/*e*):393.7 [M^+], calc. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56 %, found: C, 70.24; H, 5.91; N, 3.54 %.

*3-[5-(3-Chloro-4-fluoro-phenylamino)-pentyloxy]-1-hydroxy-9H-xanthen-9-one (**7f**)*

The compound **5** with 3-chloro-4-fluoro-phenylamine (**6f**) was yielded as a brown solid, IR (KBr, ν_{max} cm^{-1}): 3419.55 ($O–H_{stretch}$), 3264.89 ($N–H_{stretch}$), 3092.48 ($C–H_{stretch}$ Ar), 1629.85 ($C=O_{stretch}$), 1591.27 ($N–H_{bend}$), 1548.68 and 1489.05 ($C=C_{stretch}$ Ar. ring), 1392.61 ($O–H_{bend}$), 1155.36 ($C–F_{stretch}$), 1127.96 ($C–O_{stretch}$ ether), 746.45 ($C–Cl_{stretch}$), H^1 NMR (400 MHz, DMSO-d_6): δ 7.67 (d, 1H arom., $J = 9.8$ Hz), 7.43 (*t*, 1H arom., $J = 9.8$ Hz), 7.16 (*t*, 1H, $J = 9.8$ Hz), 7.12 (d, 1H arom., $J = 9.8$ Hz), 6.69 (d, 1H arom., $J = 9.8$ Hz), 6.42 (s, 1H arom.), 6.29 (d, 1H arom., $J = 9.8$ Hz), 6.12 (s, 1H arom.), 6.06 (s, 1H arom.), 5.53 (s, 1H, OH), 4.12 (*t*, 1H, $J = 2.6$ Hz, NH), 3.96 (*t*, 2H, $J = 7.32$ Hz, CH_2 near O), 3.07 (q, 2H, $J = 7.32$ Hz, CH_2 near N), 1.71 (m, 2H, $J = 7.32$ Hz, CH_2), 1.53 (m, 2H, $J = 7.32$ Hz, CH_2), 1.31 (m, 2H, $J = 7.32$ Hz, CH_2), C^{13} NMR (400 MHz, DMSO-d_6): δ 182.19 (CO), 162.51, 162.32, 157.72, 155.69 (4 × quat. arom. C), 151.2 (arom. CF), 144.6 (quat. arom. C), 132.21, 130.02 (2 × arom. CH), 121.6 (arom. CCl), 121.58 (arom. CH), 121.04 (quat. arom. C), 117.71, 117.2, 115.52, 113.2 (4 × arom. CH), 101.63 (quat. arom. C), 96.06, 94.92 (2 × arom. CH), 68.9 (CH_2 near O), 45.12 (CH_2 near N), 30.21, 29.4, 23.4 (3 × CH_2), mass (*m*/*e*): 441.1 [M^+], 443.11[M+2]$^+$ (32.1 %), calc. for $C_{24}H_{21}ClFNO_4$: C, 65.23; H, 4.79; N, 3.1 %, found: C, 65.21; H, 4.82; N, 3.20 %.

*1-Hydroxy-3-[5-(4-nitro-phenylamino)-pentyloxy]-9H-xanthen-9-one (**7g**)*

The compound **5** with 4-nitro-phenylamine(**6g**) was yielded as a yellow solid, IR (KBr, ν_{max} cm^{-1}): 3481.51 ($O–H_{stretch}$), 3361.93 ($N–H_{stretch}$), 3070.68 ($C–H_{stretch}$ Ar.), 1629.85 ($C=O_{stretch}$), 1593.20 ($N–H_{bend}$), 1553.43 and 1487.12 ($C=C_{stretch}$ Ar. ring), 1390.68 ($C–N_{stretch}$ nitro), 1129.08 (C–O_{stretc} ether), H^1 NMR (400 MHz, DMSO-d_6): δ 7.97 (2 × d, 1H arom. near NO_2, $J = 9.56$ Hz), 7.69 (d, 1H arom., $J = 9.56$ Hz), 7.43 (*t*, 1H arom., $J = 9.56$ Hz), 7.09 (*t*, 1H arom., $J = 9.56$ Hz), 7.02 (d, 1H arom., $J = 9.56$ Hz), 6.69 (2 × d, 1H arom., $J = 9.56$ Hz), 6.1 (s, 1H arom.), 6.04 (s, 1H arom.), 5.06 (s, 1H, OH), 4.14 (*t*, 1H, $J = 3.49$ Hz, NH), 3.98 (*t*, 2H, $J = 6.4$ Hz, CH_2 near O), 3.07 (q, 2H, $J = 6.4$ Hz, CH_2 near N), 1.73 (m, 2H, $J = 6.4$ Hz, CH_2), 1.53 (m, 2H, $J = 6.4$ Hz, CH_2), 1.28 (m, 2H, $J = 6.4$ Hz, CH_2), C^{13} NMR (400 MHz, DMSO-d_6): δ 182.21 (CO), 162.51, 162.32, 157.73, 155.72, 153.7, 136.81 (6 × quat. arom. C), 132.23, 130.02, 121.9, 121.63 (5 × arom. CH), 121.02 (quat. arom. C), 117.21, 114.42 (3 × arom. CH), 101.63 (quat. arom. C), 96.01, 94.93 (4 × arom. CH), 68.9 (CH_2 near of O), 45.11 (CH_2 near of N), 31.2, 29.4, 23.41 (3 × CH_2), mass (*m*/*e*): 335.6 [M^+], calc. for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10, N, 6.45 %, found: C, 66.32, H, 5.11, N, 6.48 %.

*1-Hydroxy-3-[5-(piperidin-1-yl) pentyloxy]-9H-xanthen-9-one (**7h**)*

The compound **5** with piperidine (**6h**) was yielded as a brown solid, IR (KBr, ν_{max} cm^{-1}): 3473.31 ($O–H_{stretch}$), 3091.46 ($C–H_{stretch}$ Ar), 2947.24 ($C–H_{stretch}$, Alkyl), 1646.56 ($C=O_{stretch}$), 1602.32 and 1569.12 ($C=C_{stretch}$ Ar), 1406.03 ($C–N_{stretch}$,), 1127.32 ($C–O_{stretch}$ ether), H^1 NMR (400 MHz, DMSO-d_6): δ 7.66 (d, 1H arom, $J = 7.2$ Hz), 7.42 (*t*, 1H arom, $J = 7.2$ Hz), 7.09 (*t*, 1H arom, $J = 7.2$ Hz), 7.03 (d, 1H arom, $J = 7.2$ Hz), 6.1 (s, 1H arom.), 6.04 (s, 1H arom.), 5.32 (s, 1H, OH), 3.28 (*t*, 2H, $J = 6.4$ Hz, CH_2 near of O), 2.36 (*t*, 2H, $J = 6.4$ Hz, CH_2 near of N), 2.25 (*t*, 2H, $J = 6.4$ Hz, CH_2 near of N), 1.7 (m, 2H, $J = 6.4$ Hz, CH_2), 1.51 (m, 2H, $J = 6.4$ Hz, CH_2), 1.39 (m, 2H, $J = 6.4$ Hz, CH_2), 1.29 (m, 2H, $J = 6.4$ Hz, CH_2), C^{13} NMR (400 MHz, DMSO-d_6): δ 182.21 (CO), 162.5, 162.31, 157.74, 155.72 (4 × quat. arom. C), 132.23, 131.02, 121.62 (3 × arom. CH), 121.03 (quat. arom. C), 117.21 (arom. CH), 101.62 (quat. arom. C), 96.01, 94.9 (2 × arom. CH), 68.91 (CH_2 near of O), 54.63, 54.42 (3 × CH_2 near of N), 29.4, 28.41, 25.93, 25.5, 23.71 (6 × CH_2), mass (*m*/*e*): 381.19 [M^+], calc. for $C_{23}H_{27}NO_4$: C, 72.42, H, 7.13, N, 3.67 %, found: C, 72.38, H, 7.18, N, 3.65 %.

*3-[5-(1H-Imidazol-1-yl) pentyloxy]-1-hydroxy-9H-xanthen-9-one (**7i**)*

The compound **5** with imidazole (**6i**) was yielded as a yellow solid, IR (KBr, ν_{max} cm^{-1}): 3474.65 ($O–H_{stretch}$), 3094.67 ($C–H_{stretch}$ Ar), 2948.14 ($C–H_{stretch}$ alkyl), 1666.39 ($C=O_{stretch}$), 1563.65 and 1507.24 ($C=C_{stretch}$ Ar), 1408.43 ($C–N_{stretch}$), 1123.16 ($C–O_{stretch}$ ether), H^1 NMR (400 MHz,

DMSO-d_6): δ 7.6 (d, 1H arom., $J = 3.31$ Hz), 7.56 (s, 1H arom.), 7.42 (*t*, 1H arom., $J = 9.76$ Hz), 7.09 (*t*, 1H arom., $J = 9.76$ Hz), 7.06 (d, 1H arom., $J = 9.76$ Hz), 7.01 (d, 1H arom., $J = 9.76$ Hz), 6.96 (d, 1H arom., $J = 9.76$ Hz), 6.09 (s, 1H arom.), 6.05 (s, 1H arom.), 5.24 (s, 1H, OH), 3.98 (*t*, 2H, $J = 1.9$ Hz, CH_2 near O), 3.68 (*t*, 2H, $J = 1.9$ Hz, CH_2 near N), 1.79 (m, 2H, $J = 2.3$ Hz, CH_2), 1.73 (m, 2H, $J = 2.3$ Hz, CH_2), 1.27 (m, 2H, $J = 2.3$ Hz, CH_2), C^{13} NMR (400 MHz, DMSO-d_6): δ 182.21 (CO), 162.5, 162.3, 157.71, 155.72 (4 × quat. arom. C), 136.82, 132.22, 130.03, 128.1, 121.62 (5 × arom. CH), 121.02 (quat. arom. C), 120.73, 117.22 (2 × arom. CH), 100.62 (quat. arom. C), 96.01, 94.92 (2 × arom. CH), 68.91 (CH_2 near of O), 52.43 (CH_2 near of N), 31.1, 29.4, 23.5 (3 × CH_2), mass (*m/e*): 364.14 [M^+], calc. for $C_{21}H_{20}N_2O_4$: C, 69.22, H, 5.53, N, 7.69 %, found: C, 69.23, H, 5.50, N, 7.67 %.

*3-[5-(Diisopropylamino) pentyloxy]-1-hydroxy-9H-xanthen-9-one (**7j**)*

The compound **5** with diisopropylamine (**6j**) was yielded as a gray solid, IR (KBr, ν_{max} cm^{-1}): 3473.31 ($O–H_{stretch}$); 3098 ($C–H_{stretch}$ Ar.), 2939.49 ($C–H_{stretch}$ Alkyl), 1646.56 ($C=O_{stretch}$), 1589.12 ($C=C_{stretch}$ Ar. ring), 1406.03 ($C–N_{stretch}$), 1125.52 ($C–O_{stretch}$ ether); H^1 NMR (400 MHz, DMSO-d_6): δ 7.61 (d, 1H arom., $J = 7.1$ Hz), 7.36 (*t*, 1H arom., $J = 7.1$ Hz), 7.09 (*t*, 1H arom., $J = 7.1$ Hz), 7.01 (d, 1H arom., $J = 7.1$ Hz), 6.1 (s, 1H arom.), 6.07 (s, 1H arom.), 5.13 (s, 1H, OH), 3.97 (*t*, 2H, $J = 0.6$ Hz, CH_2 near O), 2.97 (2 × m, 1H, $J = 1.2$ Hz, $CH(CH_3)_2$), 2.37 (*t*, 2H, $J = 4.37$ Hz, CH_2 near N), 1.72 (m, 2H, $J = 4.37$ Hz, CH_2), 1.39 (m, 2H, $J = 4.37$ Hz, CH_2), 1.26 (m, 2H, $J = 4.37$ Hz, CH_2), 1.08 (4 × d, 12H, $J = 1.18$ Hz, CH_3), C^{13} NMR (400 MHz, DMSO-d_6): δ 182.21 (CO), 162.52, 162.3, 157.73, 155.7 (4 × quat. arom. C), 132.23, 129.9, 121.61 (3 × arom. CH), 121.02 (quat. arom. C), 117.21 (arom. CH), 101.62 (quat. arom. C), 96.03, 95.01, 68.92 (CH_2 near of O), 49.12 (3 × CH_2 near of N), 29.4, 29.01, 23.72 (3 × CH_2), 22.91 (4 × CH_3), mass (*m/e*): 381.19 [M^+], calc. for $C_{24}H_{31}NO_4$: C, 66.35; H, 5.10, N, 6.45 %, found: C, 66.32, H, 5.11, N, 6.48 %.

Antibacterial activity

Preparation of seed of organisms

About 13.0 g of nutrient broth medium was suspended in 1,000 ml distilled water. Then, it was boiled to dissolve the medium completely and filtered from 5 μ sintered glass filter. A set of test tubes with nutrient broth (5 ml) was capped with cotton plugs and sterilized by autoclaving at 15 psig pressure (121 °C) for 15 min. Then, after cooling, a loop of various organisms were inoculated into liquid broth and incubated at 37 ± 1 °C and used within 12 h. The inoculums size for test strain was adjusted to 10^8 CFU/ml (colony forming unit per milliliter) by comparing the turbidity.

Determination of zone of inhibition

The zones of inhibition of all the synthesized compounds (**7a–j**) were determined preliminarily for antibacterial

Table 2 The zone of inhibition of synthesized compounds

Zone of inhibition (mm)[a,b]						
Compound	Gram-positive organisms			Gram-negative organisms		
	B. subtilis	*B. cereus*	*S. aureus*	*E. coli*	*P. aeruginosa*	*P. mirabilis*
7a	–[c]	–	10 ± 0.372	11 ± 0.421	13 ± 0.37	15 ± 0.35
7b	12 ± 0.25	–		–	–	–
7c	–	–	–	19 ± 0.3	11 ± 0.315	–
7d	10 ± 0.34	–	–	–	–	–
7e	9 ± 0.257	–	12 ± 0.39	–	–	–
7f	–	16 ± 0.341	14 ± 0.254	–	11 ± 0.421	19 ± 0.352
7g	18 ± 0.35	–	19 ± 0.37		16 ± 0.247	–
7h	–	–	–	11 ± 0.421	10 ± 0.34	–
7i	11 ± 0.421	–	10 ± 0.34	–	11 ± 0.421	–
7j	10 ± 0.34	11 ± 0.421	11 ± 0.421	10 ± 0.34	11 ± 0.421	–
Ofloxacin	20 ± 0.32	23 ± 0.25	21 ± 0.4	22 ± 0.4	21 ± 0.362	24 ± 0.274

[a] DMSO as negative control

[b] Data are mean of three replications

[c] No inhibition was observed

Table 3 Minimum inhibitory concentration (MIC) of synthesized compounds

MIC (μg ml^{-1})[a]						
Compound	Gram-positive organisms			Gram-negative organisms		
	B. subtilis	*B. cereus*	*S. aureus*	*E. coli*	*P. aeruginosa*	*P. mirabilis*
7a	–[b]	–	–	16	32	8
7b	32	8	–	–	–	–
7c	–	–	–	4	32	–
7d	16	–	–	–	–	–
7e	32	–	32	–	–	–
7f	–	4	8	–	16	4
7g	8	–	8	–	4	–
7h	–	–	–	16	32	–
7i	16	–	8	–	16	–
7j	8	16	16	8	16	–
Ofloxacin	2	<2	<2	<2	<2	2

[a] DMSO as negative control

[b] No antibacterial activity

screening by disk-diffusion method (Kirby–Bauer method) as recommended by Clinical and Laboratory Standards Institute document M2-A9 [ISBN 1-56238-586-0]. Petri dish containing 15 ml of Mueller–Hinton Agar (Hi-Media) was used for all the bacteria strains. 0.1 ml of seed of various organisms was aseptically inoculated over the sterile solid agar medium. Whatman no. 1 filter paper disks (6 mm in diameter) impregnated with the synthesized compound (10 μg/disk) dissolved in DMSO was placed on the plates. Ofloxacin (10 μg/disk, Hi-Media) was used as positive control for bacterial strains. A paper disk impregnated with DMSO was used as negative control. All the prepared plates were then incubated at 37 ± 1 °C for 24 h. The zone of inhibition on agar plate was measured in millimeters (mm) with a milimetric ruler, and the average of triplicate results were taken as final reading (Table 2).

Determination of minimum inhibitory concentration

Compounds that displayed favorable zone of inhibition were considered for the assessment of MIC by broth dilution method recommended by European committee for antibacterial susceptibility testing standards (Kahlmeter *et al.*, 2006). MIC of a compound is defined as the lowest concentration at which it completely inhibits visible growth (turbidity on liquid media). Solutions of the synthesized compounds with concentrations used range from 512 to 2 μg/ml of the same in a twofold dilution. DMSO was used as negative control and ofloxacin 512–2 μg/ml concentration as positive control also in a twofold dilution. Then, the seeds of organisms were incubated into various previously prepared broths with drugs. At the end of the incubation period (37 ± 1 °C for 24 h), the MIC values were determined which are presented in Table 3.

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