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Acid-catalyzed ring opening in 2-(2-hydroxynaphthalene-1-yl)-pyrrolidine-1-carboxamides: formation of dibenzoxanthenes, diarylmethanes, and calixarenes

A.S. Gazizov *, A.V. Smolobochkin, J.K. Voronina, A.R. Burilov, M.A. Pudovik

A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences, 8 Arbuzova Str., Kazan, Russian Federation

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ABSTRACT

2-(2-Hydroxynaphthalene-1-yl)pyrrolidine-1-carboxamides undergo ring opening in the presence of trifluoroacetic acid and 2-naphthol leading to the formation of new substituted dibenzoxanthenes. Reaction of 2-(2-hydroxynaphthalene-1-yl)pyrrolidine-1-carboxamides with polyatomic phenols at the same conditions was found leading to diarylmethane derivatives and calix[4]resorcinols with naphthyl fragment acting as a leaving group.

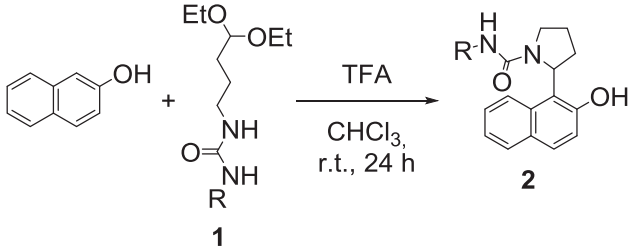
1. Introduction

Xanthene and, in particular, benzoxanthene derivatives are of considerable interest for synthetic chemists due to their antibacterial,[1–3] antiviral,[4] and anti-inflammatory[5] properties. In addition, these compounds can be used as dyes,[6,7] active laser media,[8–10] as well as pH-sensitive fluorescent probes for the study of biological objects.[11,12] A broad series of benzoxanthene derivatives containing various aryl,[13–16] hetaryl,[17–20] and alkyl substituents[15,16] in pyran ring have been synthesized. However, despite intensive studies in this field, only small number of publications are devoted to the synthesis of alkyl-substituted benzoxanthenes with functional groups in the alkyl chain. In particular, the synthesis of sulfur[21] and selenium-containing benzoxanthenes[21,22] and benzoxanthenes having hydroxyl,[23] carboxylic groups,[24,25] as well as multiple bonds[26,27] in alkyl substituent, have been described. In addition, there are a series of works of French authors,[28–30] which describe the synthesis of benzoxanthenes having methyl and ethylaminoalkyl substituents.

The principal method for the synthesis of benzoxanthenes is acid-catalyzed reaction of naphthols with aldehydes and acetals.[13–20] The range of reacting carbonyl compounds is broad and involves aromatic,[13–16] heteroaromatic,[17–20] and aliphatic aldehydes.[15,16]

2. Results

Recently, we have studied the reaction of 2-naphthol with (4,4-diethoxyethylbutyl)urea derivatives and it was shown that the products of this reaction are heterocyclic compounds, namely, 2-arylpyrrolidine derivatives **2**. We did not notice the formation of corresponding benzoxanthenes, even upon the use of an excess of 2-naphthol[31] (Scheme 1).



R = H, Ph, *p*-MeO-C_6H_4, *p*-Br-C_6H_4, *p*-NO_2-C_6H_4

Scheme 1. Reaction of 2-naphthol with (4,4-diethoxyethylbutyl)urea derivatives.

* Corresponding author. Tel./fax: +7 843 272 7324; e-mail address: agazizov@iopc.ru (A.S. Gazizov).

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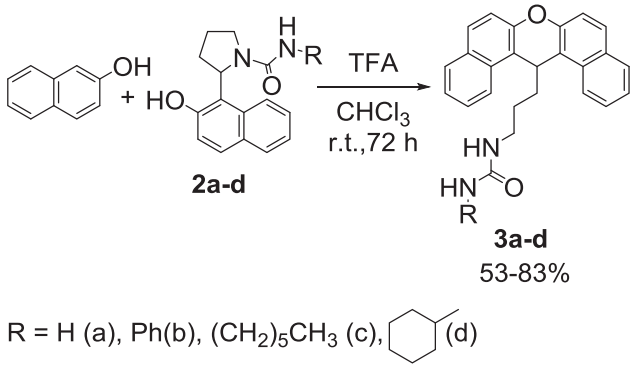
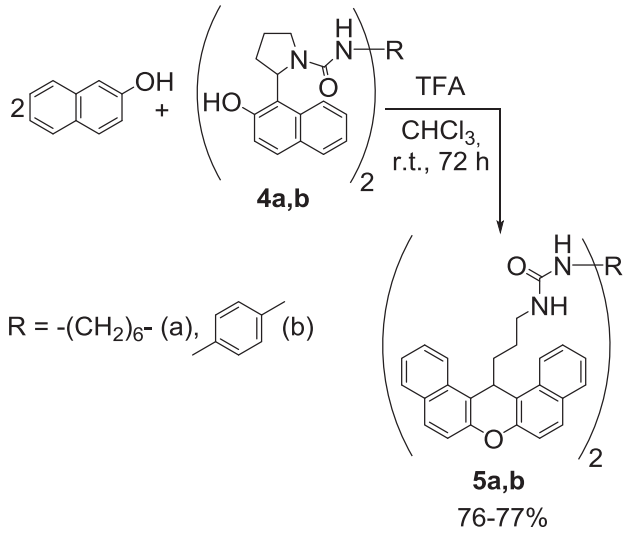
A literature survey revealed only one work,[32] where the pyrrolidine ring opening is described in *N*-phenacyl-2-phenylpyrrolidine under the action of trifluoromethanesulfonicacid. Based on these data, we suggested that the pyrrolidine ring in compounds **2** can also open under the action of strong acids.

We chose 2-(2-hydroxynaphthalene-1-yl)-pyrrolidine-1-carboxamide **2a** as a model compound.[31] The study of the reaction of compound **2**a with 2-naphthol in chloroform with trifluoroacetic acid showed that pyrrolidine ring opening proceeds under these conditions with the formation of dibenzoxanthene **3**a, which contains a urea fragment. Optimization of the reaction conditions showed that the highest yield of the target dibenzoxanthene is achieved upon use of 3 equiv of naphthol and 3 equiv of trifluoroacetic acid (Scheme 2).

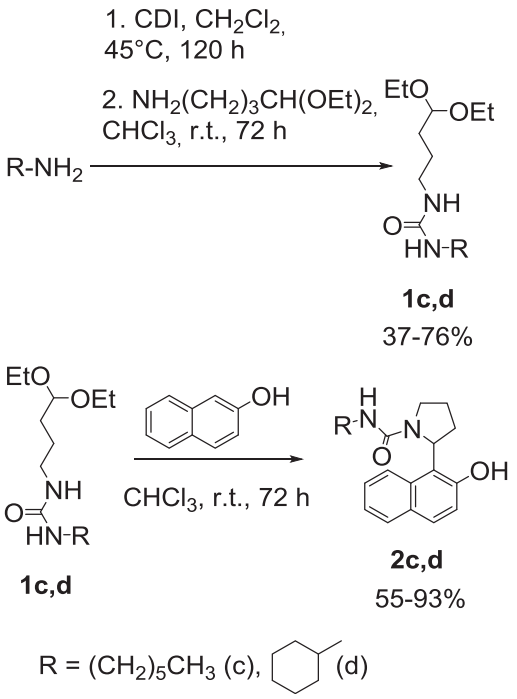




Scheme 2. Synthesis of dibenzoxanthenes **3** and bis(dibenzoxanthenes) **5**.

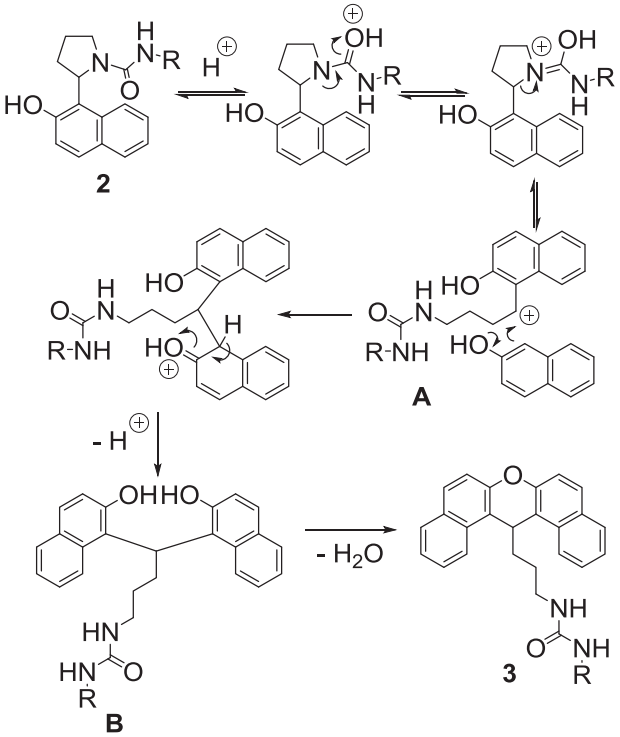
Subsequent studies revealed that the reactions of 2-naphthol with pyrrolidine-1-carboxamides **2b**–**d** having aryl, alkyl, and cycloalkyl substituents in urea fragment proceed similarly (Scheme 2). Starting compounds **2c**,**d** were synthesized in accordance with Scheme 3; the synthesis of compound **2b** was described elsewhere.[31] It should be noted that the highest yields were achieved in the case of pyrrolidine-1-carboxamides **2b**,**d** having phenyl and cyclohexyl substituents, respectively. The reactions of compounds **4a**,**b**[31] containing two pyrrolidine fragments with 6 equiv of 2-naphthol under identical conditions also gave bis(dibenzoxanthenes) **5a**,**b** (Scheme 2).

Scheme 4 illustrates proposed mechanism of this reaction, which includes protonation of urea fragment in pyrrolidine-1-



Scheme 3. Synthesis of starting 2-(2-hydroxynaphthalene-1-yl)-pyrrolidine-1-carboxamides **2c**,**d**.

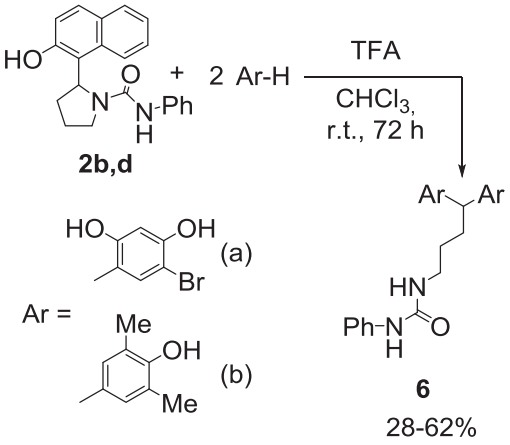
carboxamide **2**, followed by N–C bond cleavage. Carbocation **A** thus formed then reacts with naphthol molecule to give (4,4-bis(2-hydroxynaphthalen-1-yl)butyl)urea derivative **B**. Finally, elimination of water molecule from this intermediate compound leads to the formation of dibenzoxanthene**3**. It should be noted that in previously published work, a 10-fold excess of triflic acid was needed to open the pyrrolidine ring in *N*-phenacyl-2-



Scheme 4. Proposed mechanism for the formation of dibenzoxanthenes.

phenylpyrrolidines.[32] However, in our case, trifluoroacetic acid taken at only three-fold excess was enough. This may be attributed to higher basicity of ureas compared to acid amides,[33] which facilitates the initial protonation of urea. Also 2-hydroxynaphtyl group stabilizes intermediate carbocation **A** more effectively than less electron-rich phenyl group and thus, favors ring-opening.

The possibility of using other phenols in this reaction and thus, preparation of unsymmetrical benzoxanthenes was also of interest for us. For this purpose, we studied the reaction of pyrrolidine-1-carboxamide **2b** with 4-bromoresorcinol. The reaction of compound **2b** with 1 equiv of 4-bromoresorcinol gave a complex mixture of products and we did not succeed in isolating any individual compound. Performing the reaction with a three-fold excess of 4-bromoresorcinol gave unexpectedly the polyphenol **6a**, which contains two resorcinol fragments, in 28% yield (Scheme 5). Further studies showed that the interaction of 2,6-dimethylphenol with pyrrolidine-1-carboxamide **2b** also leads to the formation of polyphenolic compound **6b**.

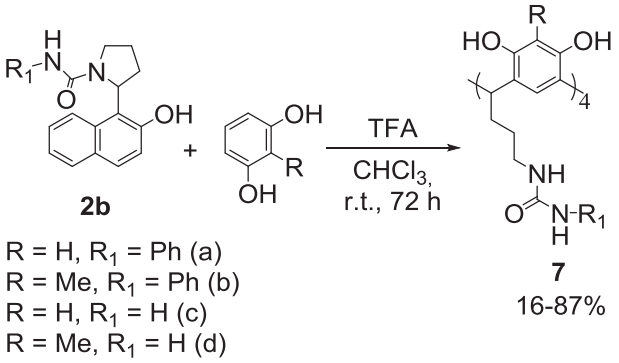


Scheme 5. Reaction of pyrrolidine-1-carboxamide **2b** with phenols.

Analysis of the literature revealed that the carbon–carbon bond cleavage in (2-hydroxynaphtyl)methane derivatives in acidic media is known.[34–36] Thus, this reaction turned out to be unsuitable for the synthesis of unsymmetrical benzoxanthenes.

It should be noted that the most common way of synthesis of dimeric polyphenols,[37,38] as well as calix[4]resorcinols,[39,40] is the reaction of appropriately substituted acetals or aldehydes with phenols in acidic media. However, this method cannot be used in the case of acetals containing urea fragment, since they undergo intramolecular cyclization in these conditions, giving rise to heterocyclic compounds.[41–43] Thus, we decided to further investigate this reaction and check its applicability to the synthesis of calix[4] resorcinols containing urea substituent.

The reaction of pyrrolidine-1-carboxamide **2b** with a three-fold excess of resorcinol and 2-methylresorcinol in chloroform gave a mixture of products. The analysis of the reaction mass via mass-spectrometry showed that there are both dimer compounds and macrocyclic polyphenols, calix[4]resorcinols. Carrying out the reaction of compound **2b** with these phenols taken at an equimolar amount allowed us obtaining macrocycles **7a**,**b** as the main product in 87 and 74% yield correspondingly (Scheme 6). Reaction of pyrrolidine-1-carboxamide **2a** with resorcinol and 2-methylresorcinol proceeds similarly and leads to the formation of macrocycles **7c**,**d**, although the yields are lower in this case. Interestingly, there is signals of acetone in the NMR spectra of compound **7c** (approx. 0.5 mol per 1 mol of calixarene) even after prolonged heating in vacuum; probably, this is due to host–guest complex formation.



Scheme 6. Synthesis of calixarenes **7**.

The structure of compound **7b** was also confirmed by X-ray analysis data (Fig. 1). Analyzed crystals of compound **7b** are the crystalline solvates with DMSO and water in a ratio of 1.5:1. X-ray structure analysis revealed that the calixarene is in the cone conformation, bond lengths, and angles in the molecule of compound **7b** in crystals are within the standard limits for each type of chemical bond. The molecular packing in this crystal is formed by the classic O–H···O and N–H···O hydrogen bonds both between calixarene molecules and with the participation of solvent molecules.

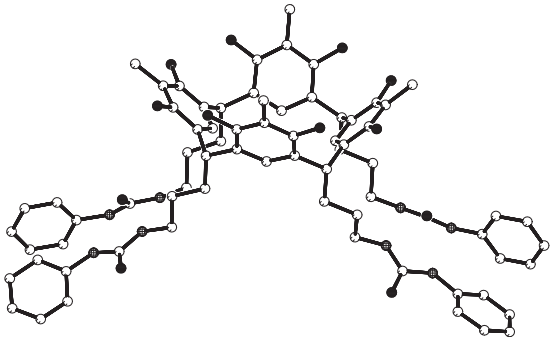


Fig. 1. X-ray structure of calixarene **7**.

3. Conclusion

We have developed a new method for the synthesis of dibenzoxanthenes modified with urea fragments, which is based on the acid-catalyzed opening of the pyrrolidine ring in pyrrolidine-1-carboxamides in the presence of naphthol. In addition, a new reaction of 2-(2-hydroxynaphthalene-1-yl)pyrrolidine-1-carboxamides with polyatomic phenols, which leads to the formation of linear and macrocyclic polyphenols, where naphthyl fragment acts as a leaving group, was discovered.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Bruker MSL 400 spectrometer (working frequency 400.13 MHz) in $(CD_3)_2SO$ relative to the residual solvent protons. ^{13}C NMR spectra were recorded on Bruker Avance 600 spectrometer (working frequency 150.90 MHz). The MALDI-TOF mass spectra were recorded on a Bruker ULTRAFLEX III TOF/TOF instrument (with 2,5-dihydroxybenzoic acid matrix). IR spectra were obtained with a Bruker Vector 22 spectrometer. Elemental analysis was performed on Carlo Erba EA 1108 instrument.

Melting points were determined in glass capillaries with a Stuart SMP 10 apparatus. Single-crystal X-ray diffraction analysis was performed at 295(2) K on Smart Apex II automatic diffractometer using graphite monochromated radiation. All solvents were purified and dried according to standard procedures.

4.2. Synthesis of xanthenes 3

To a solution of 2-napthol (0.17 g, 1.17 mmol) in 10 ml of dry chloroform pyrrolidine-1-carboxamide **2** (0.39 mmol) and trifluoroacetic acid (0.13 g, 1.17 mmol) was added. The mixture was stirred at room temperature for 72 h. Solvent was evaporated in vacuo, residue was washed with diethyl ether, filtered, and dried in vacuo (1 h, 0.01 Torr) to give the title compound **3**.

*4.2.1. 1-(3-(14H-Dibenzo[a,j]xanthen-14-yl)propyl)urea (**3a**).* White solid. Yield 0.079 g (53%). Mp: 177–178 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 0.94–1.04 (2H, m, CH_2), 1.85–1.94 (2H, m, CH_2), 2.59–2.68 (2H, m, CH_2), 5.69–5.75 (1H, m, CH), 7.44 (2H, d, *J* 8.9 Hz, CH_{Ar}), 7.48–7.54 (2H, m, CH_{Ar}), 7.65–7.71 (2H, m, CH_{Ar}), 7.90 (2H, d, *J* 8.9 Hz, CH_{Ar}), 7.94–7.99 (2H, m, CH_{Ar}), 8.52–8.57 (2H, m, CH_{Ar}). ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 26.3, 30.3, 33.9, 39.8, 117.0, 117.6, 123.5, 124.9, 127.4, 128.9, 129.1, 131.1, 131.5, 149.9, 158.8. IR (KBr): 1592, 1651, 2937, 3066, 3329 cm^{-1}. Anal. Calcd (%) for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.82; H, 5.97; N, 7.04. MALDI TOF, *m*/*z*: 405 [M+Na]$^+$.

*4.2.2. 1-(3-(14H-Dibenzo[a,j]xanthen-14-yl)propyl)-3-phenylurea (**3b**).* White solid. Yield 0.14 g (78%). Mp: 240–241 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 1.00–1.11 (2H, m, CH_2), 1.89–1.99 (2H, m, CH_2), 2.71–2.79 (2H, m, CH_2), 5.72–5.77 (1H, m, CH), 5.81–8.84 (1H, m, NH), 6.82 (1H, t, *J* 7.1 Hz, CH_{Ar}), 7.13 (2H, t, *J* 8.2 Hz, CH_{Ar}), 7.23 (2H, d, *J* 7.8 Hz, CH_{Ar}), 7.44 (2H, d, *J* 8.9 Hz, CH_{Ar}), 7.49–7.54 (2H, m, CH_{Ar}), 7.65–7.71 (2H, m, CH_{Ar}), 7.91 (2H, d, *J* 8.9 Hz, CH_{Ar}), 7.96–8.00 (2H, m, CH_{Ar}), 8.15 (1H, br s, NH), 8.54–8.59 (2H, m, CH_{Ar}). ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 26.3, 30.3, 33.9, 39.5, 117.0, 117.6, 118.0, 121.3, 123.6, 124.9, 127.4, 129.0, 129.1, 131.1, 131.5, 140.9, 149.9, 155.3. IR (KBr): 1592, 1650, 2937, 3065, 3328 cm^{-1}. Anal. Calcd (%) for $C_{31}H_{26}N_2O_2$: C, 81.20; H, 5.72; N, 6.11. Found: C, 81.46; H, 5.58; N, 5.93. MALDI TOF, *m*/*z*: 481 [M+Na]$^+$.

*4.2.3. 1-(3-(14H-Dibenzo[a,j]xanthen-14-yl)propyl)-3-hexylurea (**3c**).* White solid. Yield 0.09 g (53%). Mp: 183–184 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 0.83 (3H, t, *J* 7.04 Hz, CH_3), 0.91–1.02 (2H, m, CH_2), 1.08–1.27 (8H, m, CH_2), 1.84–1.93 (2H, m, CH_2), 2.59–2.67 (2H, m, CH_2), 2.76–2.83 (2H, m, CH_2), 5.42–5.51 (2H, m, NH), 5.69–5.74 (1H, m, CH),7.43 (2H, d, *J* 8.9 Hz, CH_{Ar}), 7.47–7.54 (2H, m, CH_{Ar}), 7.64–7.70 (2H, m, CH_{Ar}), 7.91 (2H, d, *J* 8.9 Hz, CH_{Ar}), 7.94–7.99 (2H, m, CH_{Ar}), 8.51–8.56 (2H, m, CH_{Ar}). ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 14.3, 15.6, 22.5, 26.4, 26.5, 26.5, 30.3, 31.4, 33.9, 39.4, 117.0, 117.6, 123.5, 124.8, 127.3, 128.9, 129.1, 131.1, 131.5, 149.8, 158.2. IR (KBr): 1592, 1625, 2857, 2927, 3069, 3417 cm^{-1}. Anal. Calcd (%) for $C_{31}H_{34}N_2O_2$: C, 79.79; H, 7.34; N, 6.00. Found: C, 79.88; H, 7.12; N, 6.26. MALDI TOF, *m*/*z*: 489 [M+Na]$^+$.

*4.2.4. 1-(3-(14H-Dibenzo[a,j]xanthen-14-yl)propyl)-3-cyclohexylurea (**3d**).* White solid. Yield 0.15 g (83%). Mp: 246–247 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 0.84–1.00 (4H, m, CH_2), 1.02–1.22 (3H, m, CH_2), 1.41–1.49 (1H, m, CH_2), 1.50–1.61 (4H, m, CH_2), 1.85–1.93 (2H, m, CH_2), 2.59–2.67 (2H, m, CH_2), 3.10–3.21 (1H, m, CH_2), 5.35–5.39 (1H, m, CH), 5.39 (1H, br s, NH), 5.69–5.74 (1H, m, CH), 7.43 (2H, d, *J* 8.8 Hz, CH_{Ar}), 7.49–7.54 (2H, m, CH_{Ar}), 7.65–7.70 (2H, m, CH_{Ar}), 7.91 (2H, d, *J* 8.8 Hz, CH_{Ar}), 7.95–8.00 (2H, m, CH_{Ar}), 8.52–8.56 (2H, m, CH_{Ar}). ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 24.9, 25.7, 26.5, 30.3, 33.7, 33.9, 39.8, 48.0, 117.0, 117.6, 123.6, 124.9, 127.3, 128.9, 129.1, 131.1, 131.5, 149.8, 157.5. IR (KBr): 1593, 1635, 2853, 2935, 3069 cm^{-1}. Anal. Calcd (%) for $C_{31}H_{32}N_2O_2$: C, 80.14; H, 6.94; N, 6.03. Found: C, 79.92; H, 6.84; N, 6.30. MALDI TOF, *m*/*z*: 487 [M+Na]$^+$.

4.3. Synthesis of bis-xanthenes 5

To a solution of 2-napthol (0.15 g, 1.04 mmol) in 10 ml of dry chloroform bis-pyrrolidine-1-carboxamide **4** (0.17 mmol) and trifluoroacetic acid (0.12 g, 1.05 mmol) was added. The mixture was stirred at room temperature for 72 h. Solvent was evaporated in vacuo. Residue was washed with diethyl ether, filtered, and dried in vacuo (1 h, 0.01 Torr) to give the title compound **5**.

*4.3.1. 1,1′-(Hexane-1,6-diyl)bis(3-(3-(14H-dibenzo[a,j]xanthen-14-yl)propyl)urea) (**5a**).* White solid. Yield 0.10 g (76%). Mp: 245–246 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 0.91–1.00 (4H, m, CH_2), 1.02–1.09 (4H, m, CH_2), 1.10–1.22 (4H, m, CH_2), 1.83–1.93 (4H, m, CH_2), 2.58–2.67 (4H, m, CH_2), 2.73–2.82 (4H, m, CH_2), 5.45 (4H, br s, NH), 5.67–5.73 (2H, m, CH), 7.42 (4H, d, *J* 8.8 Hz, CH_{Ar}), 7.46–7.52 (4H, m, CH_{Ar}), 7.62–7.70 (4H, m, CH_{Ar}), 7.89 (4H, d, *J* 8.8 Hz, CH_{Ar}), 7.93–7.98 (4H, m, CH_{Ar}), 8.49–8.56 (4H, m, CH_{Ar}). ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 26.5, 26.5, 30.32, 33.9, 39.8, 117.0, 117.6, 123.5, 124.8, 127.3, 128.9, 129.1, 131.1, 131.5, 149.8, 158.2. IR (KBr): 1593, 1624, 2845, 2928 cm^{-1}. Anal. Calcd (%) for $C_{56}H_{54}N_4O_4$: C, 79.40; H, 6.43; N, 6.61. Found: C, 79.22; H, 6.67; N, 6.79. MALDI TOF, *m*/*z*: 870 [M+Na]$^+$.

*4.3.2. 1,1′-(1,4-Phenylene)bis(3-(3-(14H-dibenzo[a,j]xanthen-14-yl)propyl)urea) (**5b**).* White solid. Yield 0.11 g (77%). Mp: >250 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 0.99–1.09 (4H, m, CH_2), 1.87–1.97 (4H, m, CH_2), 2.66–2.76 (4H, m, CH_2), 5.66–5.71 (2H, m, CH), 5.71–5.76 (2H, m, NH), 6.99 (4H, s, CH_{Ar}), 7.44 (4H, d, *J* 8.9 Hz, CH_{Ar}), 7.47–7.53 (4H, m, CH_{Ar}), 7.64–7.70 (4H, m, CH_{Ar}), 7.90 (4H, d, *J* 8.9 Hz, CH_{Ar}), 7.94–7.99 (4H, d, *J* 8.02 Hz, CH_{Ar}), 8.53–8.58 (4H, d, *J* 8.96 Hz, CH_{Ar}). ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 26.3, 30.3, 33.9, 39.8, 117.0, 117.6, 118.8, 123.5, 124.9, 127.4, 128.9, 129.1, 131.1, 131.5, 149.9, 155.5. IR (KBr): 1592, 1652, 2857, 2937, 3065 cm^{-1}. Anal. Calcd (%) for $C_{56}H_{46}N_4O_4$: C, 80.17; H, 5.53; N, 6.68. Found: C 79.93; H 5.73; N 6.57. MALDI TOF, *m*/*z*: 861 [M+Na]$^+$.

4.4. Synthesis of dimers 6

To a mixture of 2-(2-hydroxynaphthalen-1-yl)-*N*-phenylpyrrolidine-1-carboxamide **2b** (0.1 g, 0.30 mmol) in dry chloroform (10 ml) appropriate phenol (0.90 mmol) and trifluoroacetic acid (0.1 g, 0.30 mmol) was added. The mixture was stirred at room temperature for 72 h. Solvent was evaporated in vacuo. Residue was washed with diethyl ether, filtered, and dried in vacuo (1 h, 0.01 Torr) to give the title compound **6**.

*4.4.1. 1-(4,4-Bis(5-bromo-2,4-dihydroxyphenyl)butyl)-3-phenylurea (**6a**).* White solid. Yield0.05 g (28%). Mp: 132–133 °C. ^{1}H NMR ((CD_3)$_2$SO, 400 MHz), δ (ppm): 1.27–1.37 (2H, m, CH_2), 1.77–1.86 (2H, m, CH_2), 3.02–3.10 (2H, m, CH_2), 4.25 (1H, t, *J* 7.9 Hz, CH_{Ar}), 6.08 (1H, t, *J* 5.8 Hz, NH), 6.45 (2H, s, CH_{Ar}), 6.84–6.89 (1H, m, CH_{Ar}), 7.03 (2H, s, CH_{Ar}), 7.16–7.22 (2H, m, CH_{Ar}), 7.33–7.38 (2H, m, CH_{Ar}). IR (KBr): 1597, 1652, 2868, 2937, 3402 cm^{-1}. ^{13}C NMR ((CD_3)$_2$SO, 150 MHz), δ (ppm): 29.0, 31.5, 36.1, 65.4, 98.2, 104.0, 118.1, 121.3, 124.4, 129.0, 131.7, 141.0, 152.7, 155.5, 155.6. Anal. Calcd (%) for $C_{23}H_{22}Br_2N_2O_5$: C, 48.79; H, 3.92; Br, 28.22; N, 4.95. Found: C, 48.54; H, 3.71; Br, 28.39; N, 5.12. MALDI TOF, *m*/*z*: 589 [M+Na]$^+$.

*4.4.2. 1-(3,3-Bis(4-hydroxy-3,5-dimethylphenyl)propyl)-3-phenylurea (**6b**).* White solid. Yield 0.08 g (62%). Mp: 181–182 °C.

^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz), δ (ppm): 1.42–1.50 (2H, m, CH$_2$), 1.96–2.04 (2H, m, CH$_2$), 2.19 (12H, s, CH$_3$), 2.21–2.27 (2H, m, CH$_2$), 3.66 (1H, t, *J* 7.9 Hz, CH), 5.80–5.87 (1H, br s, NH), 6.07 (4H, s, CH$_{Ar}$), 6.88–6.93 (1H, m, CH$_{Ar}$), 6.96–6.99 (1H, br s, NH), 7.17–7.23 (2H, m, CH$_{Ar}$), 7.45–7.49 (2H, m, CH$_{Ar}$). ^{13}C NMR ((CD$_3$)$_2$CO, 150 MHz), δ (ppm): 15.9, 39.6, 49.5, 65.2, 118.3, 121.4, 123.5, 127.6, 128.5, 137.0, 140.7, 151.2, 155.5. IR (KBr): 1596, 1644, 1686, 2862, 2936, 3011, 3319, 3565. Anal. Calcd (%) for C$_{27}$H$_{32}$N$_2$O$_3$: C, 74.97; H, 7.46; N, 6.48. Found: C, 74.80; H, 7.52; N, 6.33. MALDI TOF, *m*/*z*: 432 [M]$^+$; 455 [M+Na]$^+$; 471 [M+K]$^+$.

4.5. Synthesis of calixarenes 7

To a mixture of 2-(2-hydroxynaphthalen-1-yl)-*N*-phenylpyrrolidine-1-carboxamide **2b** (0.1 g, 0.30 mmol) and appropriate phenol (0.30 mmol) in dry chloroform (5 ml) trifluoroacetic acid (0.45 g, 3.92 mmol) was added. The mixture was stirred at room temperature for 72 h. Solvent was evaporated in vacuo. Residue was washed with diethyl ether and acetone, filtered, and dried in vacuo (1 h, 0.01 Torr) to give the title compound **7**.

*4.5.1. 1,1′,1″,1‴-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octahydroxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-2,4,6,8-tetrayl)tetrakis(propane-3,1-diyl)) tetrakis(3-phenylurea) (**7a**).* White solid. Yield 0.08 g (87%). Mp: >250 °C. ^{1}H NMR (CD$_3$OH, 400 MHz), δ (ppm): 1.42–1.52 (8H, m, CH$_2$), 2.24–2.33 (8H, m, CH$_2$), 3.18–3.26 (8H, m, CH$_2$), 4.32 (4H, t, *J* 7.3 Hz, CH), 6.23 (4H, s, CH$_{Ar}$), 6.88–6.96 (4H, m, CH$_{Ar}$), 7.16–7.24 (8H, m, CH$_{Ar}$), 7.28–7.36 (12H, m, CH$_{Ar}$). ^{13}C NMR (CD$_3$OH, 150 MHz), δ (ppm): 28.8, 31.0, 33.3, 39.4, 102.8, 119.1, 122.2, 123.5, 124.0, 128.5, 139.5, 151.8, 157.1. IR (KBr): 1598, 1653, 2866, 2935, 3340 cm^{-1}. Anal. Calcd (%) for C$_{68}$H$_{72}$N$_8$O$_{12}$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.32; H, 6.15; N, 9.28. MALDI TOF, *m*/*z*: 1193 [M]$^+$; 1194 [M+H]$^+$; 1216 [M+Na]$^+$; 1232 [M+K]$^+$.

*4.5.2. 1,1′,1″,1‴-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octahydroxy-1^5,3^5,5^5,7^5-tetramethyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-2,4,6,8-tetrayl) tetrakis(propane-3,1-diyl))tetrakis(3-phenylurea) (**7b**).* White solid. Yield 0.07 g (74%). Mp: >250 °C. ^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz), δ (ppm): 1.43–1.59 (8H, m, CH$_2$), 2.00–2.18 (8H, m, CH$_2$), 2.04 (12H, s, CH$_3$), 2.23–2.32 (8H, m, CH$_2$), 3.18–3.28 (8H, m, CH$_2$), 4.40 (4H, t, *J* 7.80 Hz, CH), 6.90–6.96 (4H, m, CH$_{Ar}$), 7.15 (4H, s, H Ar), 7.17–7.22 (8H, m, CH$_{Ar}$), 7.27–7.34 (8H, m, CH$_{Ar}$). ^{13}C NMR ((CD$_3$)$_2$SO, 150 MHz), δ (ppm): 8.5, 28.9, 31.4, 34.3, 39.4, 112.4, 119.2, 120.0, 122.2, 124.8, 128.5, 139.4, 149.5, 157.2. IR (KBr): 1598, 1653, 2862, 2933, 3057, 3387 cm^{-1}. Anal. Calcd (%) for C$_{72}$H$_{80}$N$_8$O$_{12}$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.03; H, 6.71; N, 8.69. MALDI TOF, *m*/*z*: 1249 [M]$^+$; 1250 [M+H]$^+$; 1272 [M+Na]$^+$; 1288 [M+K]$^+$.

*4.5.3. 1,1′,1″,1‴-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octahydroxy-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-2,4,6,8-tetrayl)tetrakis(propane-3,1-diyl)) tetraurea (**7c**).* White solid. Yield 0.05 g (18%). Mp: >250 °C. ^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz), δ (ppm): 1.19–1.36 (8H, m, CH$_2$), 1.99–2.19 (8H, m, CH$_2$), 2.88–3.10 (8H, m, CH$_2$), 4.11–4.32 (4H, m, CH), 6.17 (4H, s, CH$_{Ar}$), 7.19 (4H, s, CH$_{Ar}$). ^{13}C NMR ((CD$_3$)$_2$SO, 150 MHz), δ (ppm): 29.5, 31.1, 33.4, 102.9, 123.5, 125.5, 152.2, 159.4. IR (KBr): 1597, 1654, 2861, 2929, 3056, 3371 cm^{-1}. Anal. Calcd (%) for C$_{44}$H$_{56}$N$_8$O$_{12}$: C 59.45; H 6.35; N 12.61. Found: C 59.69; H 6.15; N 12.83. MALDI TOF, *m*/*z*: 911 [M+Na]$^+$.

*4.5.4. 1,1′,1″,1‴-((1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-Octahydroxy-1^5,3^5,5^5,7^5-tetramethyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-2,4,6,8-tetrayl) tetrakis(propane-3,1-diyl))tetraurea (**7d**).* White solid. Yield 0.05 g (16%). Mp: >250 °C. ^{1}H NMR ((CD$_3$)$_2$SO, 400 MHz), δ (ppm): 1.20–1.36 (8H, m, CH$_2$), 1.95 (12H, s, Me), 2.16–2.30 (8H, m, CH$_2$), 2.98–3.08 (8H, m, CH$_2$), 4.16–4.25 (4H, m, CH), 7.27 (4H, s, CH$_{Ar}$). ^{13}C NMR ((CD$_3$)$_2$SO, 150 MHz), δ (ppm): 10.5, 29.5, 30.7, 34.7, 40.8, 112.1, 121.6, 125.1, 149.5, 159.3. IR (KBr): 1596, 1654, 2862, 2931, 3064, 3381 cm^{-1}. Anal. Calcd (%) for C$_{48}$H$_{64}$N$_8$O$_{12}$: C 61.00; H 6.83; N 11.86. Found: C 61.19; H 7.02; N 11.97. MALDI TOF, *m*/*z*: 968 [M+Na]$^+$.

4.6. X-ray diffraction study of calixarene 7b

The X-ray diffraction data for the crystals of **7** were collected on a Smart Apex II automatic diffractometer using graphite monochromated radiation. The structures were solved by direct methods and refined by full-matrix least-squares using the SHELXL97[44] program. All figures were made using programs PLATON[45] and MERCURY.[46] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 1013421. For compound C$_{82}$H$_{82}$N$_8$O$_{18}$S$_5$: *M*=1627.86, triclinic, space group P-1, *a*=13.846(11), *b*=18.260(14), *c*=20.513(15) Å, α=70.141(10), β=71.080(10), γ=68.412(10)°; *V*=4416(6) Å^3; *Z*=2; ρ_{calc}=1.224 g cm^{-3}, μ(Mo-K$_\alpha$)=0.71073 mm^{-1}, *F*(000)=1708, $2\theta_{max}$=52°, 17,173 reflections collected, 7640 observed ($I>2\sigma(I)$) reflections, 1165 refined parameters, R_1 value 0.0851, wR_2=0.1722 (all data R=0.1722, wR_2=0.3221), S=1.045, minimum and maximum transmissions 0.013 and 0.013, respectively, maximum and minimum residual electron densities +0.864 and −0.366 e Å^3.

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Supplementary data

Procedures for the synthesis of pyrrolidine-1-carboxamides **2c**,**d** and copies of ^{1}H and ^{13}C NMR spectra of all products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.12.011. These data include MOL files and InChiKeys of the most important compounds described in this article.

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