The Role of Substituents and Solvents in Promoting "Medium-Size" Ring–Chain Tautomerism

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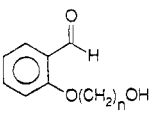
Two series of *o*-hydroxyalkoxybenzaldehydes have been examined by ^1H and ^{13}C NMR for their tendency to exhibit ring–chain tautomerism. All members of the diethylenoxy family exist as chain tautomers rather than partially or wholly as the 10-membered rings. The ethylenoxy compounds in solution are mixtures of chain and 7-membered ring tautomers in every case where a substituent is present on the aromatic ring ortho to the alkoxy group. Ring–chain equilibrium constants, determined by ^1H NMR integration of methine and formyl peaks, varied as much as 100-fold with substituents and solvent. A good correlation is noted between percent ring tautomer and the size of the ortho substituent. A second substituent para to the alkoxy group enhances K considerably, even though $K = 0$ in cases where there is only a para substituent.

Of the myriad of examples of ring–chain tautomerism among natural and synthetic compounds,[1,2] very few have been reported in which the ring is larger than 5- or 6-membered. Although there is no published account of the existence of "macro" ring tautomers (ring size 12 or larger), a few examples of "medium-size" ring tautomers have been described, where the ring is usually 7-membered. Among this rare group are some 1,4-benzodiazepines, including oxazepam;[3,4] an enamino analogue of oxazepam;[5] anthramycin[6,7] and *N*-methylanthramycin;[8] ozonolysis products from alkenylmesitylcarbinols;[9] and a hemiacetal containing the novel oxazepinium ring system.[10] In only a very few instances has it been observed that a chain and its 7-membered ring tautomer coexist at equilibrium; examples are the acetophenone hydrazone from 1-methyl-1-(*o*-aminobenzoyl)hydrazine;[11] 6-hydroxy-4-oxahexanal and 6-hydroxy-4-oxaheptanal;[12] some *A*-homocholestenes;[13] and 7-(hydroxymethyl)bicyclo[3.3.1]nonan-3-one.[14]

The number of examples of "medium-size" ring–chain tautomerism is insufficient to draw any conclusions about the effect of structure on the position of equilibrium. One system which seemed attractive for study was benzaldehydes with a hydroxy group situated on an ortho side chain. We had previously shown that benzaldehydes of the general structure **1** (n = 2, 3, 4, 11) exist solely as chain



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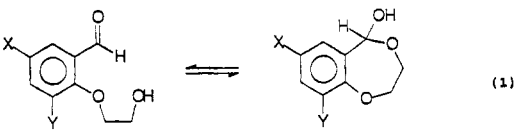
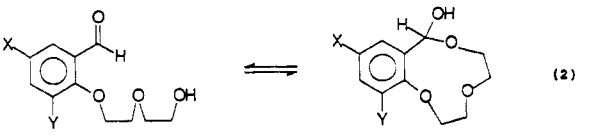
tautomers.[15] By contrast, Hullar and Failla had reported IR and NMR data which led them to describe the dichlorinated benzaldehyde **10** as solely ring tautomer in the solid state and as a ring/chain mixture in THF or DMSO.[16] This apparent influence of the aromatic substituents in controlling the ring–chain equilibrium prompted us to examine two series of compounds: *o*-(2-hydroxyethoxy)-benzaldehydes **2–11** ["ethylenoxy"] and *o*-(5-hydroxy-3-



(1)

[C] [R]

2: X = Y = H
3: X = H, Y = NO_2
4: X = H, Y = Br
5: X = H, Y = Ph
6: X = H, Y = CH_3
7: X = NO_2, Y = H
8: X = Br, Y = H
9: X = Y = Br
10: X = Y = Cl
11: X = Y = I



(2)

[C] [R]

12: X = H, Y = NO_2
13: X = H, Y = Ph
14: X = Br, Y = H
15: X = Y = Br
16: X = Y = Cl
17: X = Y = I

oxapentyloxy)benzaldehydes **12–17** ["diethylenoxy"], in which the ring tautomers would be 7- and 10-membered, respectively.

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Results and Discussion

Members of the ethylenoxy and diethylenoxy series were obtained in modest yield from the corresponding salicylaldehydes, which were alkylated in the form of their preformed salts with 2-bromoethanol or 2-(2-chloroethoxy)ethanol to afford the ethylenoxy or diethylenoxy benzaldehydes, respectively. The salicylaldehydes not commercially available were prepared by formylation of the appropriate phenols[17] or, in one instance, by bromination of salicylaldehyde.[18] The potential ring–chain tautomers of these benzaldehydes **2–17** were fully characterized by their IR, ^{1}H and ^{13}C NMR, and mass spectra. Composition was confirmed by elemental analysis of the benzaldehyde or its semicarbazone or by high-resolution MS determination of the molecular weight.

In the past, structures of ring–chain tautomers have been assigned from IR, UV, and ^{1}H NMR, but the conclusions were usually only qualitative. The lack of a carbonyl stretch in the IR, for example, has been advanced as evidence for the ring tautomer of anthramycin.[7] NMR has been used for quantitative analysis of ring–chain mixtures in only a few instances.[14,16,19] We have looked in detail at the two series of benzaldehydes by IR and ^{1}H and ^{13}C NMR spectroscopy.

The diethylenoxy benzaldehydes **12–17** are assigned exclusively the chain structures on the basis of their spectra. All showed strong C=O bands at 1660–1690 cm^{-1} in the IR spectra, as well as broad OH stretching. The ^{1}H NMR spectra are characterized by a formyl proton at 10.13–10.56 ppm and none in the region expected for the methine proton of the ring tautomer at 5–6 ppm. The aromatic protons appear with the expected multiplicities for a single tautomer; the methylene protons are unresolved multiplets. Likewise the ^{13}C NMR spectra fit the chain structures, with a formyl carbon at 188–191 ppm and four methylene and six aromatic carbons. The only exceptions are the nitro compound **12**, in which two of the methylenes and two of the aromatic carbons apparently coincide, and the phenyl compound **13** with its four additional aromatic carbons. The ^{13}C chemical shifts have been assigned by comparison with calculated values.[20–22] The mass spectra show typical fragmentation between the aryloxy ether and side chain (see supplementary material).

Unlike the diethylenoxy benzaldehydes, which show no tendency to equilibrate to the 10-membered ring tautomers, several of the ethylenoxy compounds are mixtures of chain and 7-membered ring tautomers. The qualitative evidence for ring tautomer includes a weakened or missing C=O stretch in the IR, a methine proton in the NMR at 5.6–5.9, and a carbon resonance at 94–103 ppm. The ^{1}H NMR spectra of ring–chain mixtures are typified by the presence of both aldehyde and methine protons, by a doubling of the aromatic protons, and by a more complex methylene region. The assignment of protons to each tautomer is internally consistent, as determined by relative integrations of protons assigned to the ring [R][23] (methine, aromatic) and chain [C][23] (aldehyde, aromatic). Assignment of the aromatic protons to ring and chain tautomers was confirmed by a long-range COSY (LRCOSY) experiment with the 3,5-dibromo compound **9** (see Figure 1). Cross peaks of the methinyl proton are observed with the upfield aromatic resonances, which thus must be attributed to the ring tautomer.

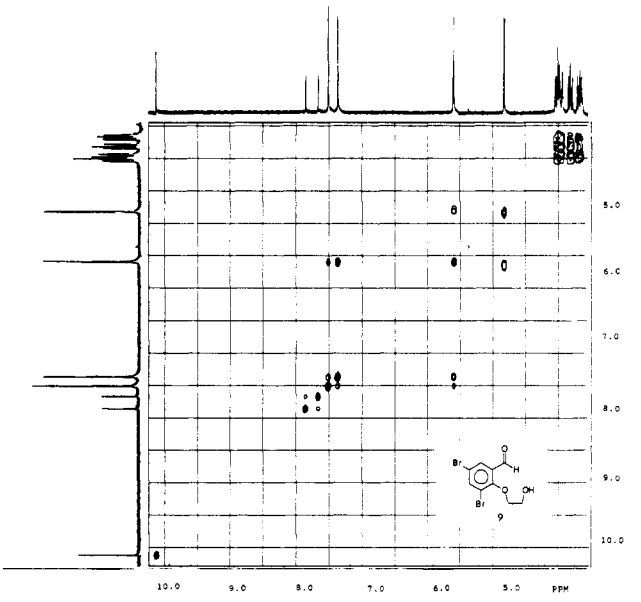

Figure 1. Long-range COSY spectrum of 3,5-dibromo-2-(2-hydroxyethoxy)benzaldehyde (**9**) in acetonitrile-d_3.

Table I. Equilibrium Constants of Substituted 2-(2-Hydroxyethoxy)benzaldehydes in Various Solvents.

substituted benzaldehydes	K(DMSO)[a]	K(CD_3CN)[a]	K($CDCl_3$)[a]
2 (H)	*b*	0	0
3 (3-NO_2)	11.4	2.9	1.6
7 (5-NO_2)	0	0	0
4 (3-Br)	1	1	1
8 (5-Br)	0	0	0
5 (3-Ph)	0.4	0.24	0.1
6 (3-CH_3)	0.6		1.0
9 (3,5-diBr)	7.1	2.3	0.9
10 (3,5-diCl)	6.8	2.1	0.7
11 (3,5-diL)	7.4	2.6	1.2

[a] K = (integration of methine proton)/(integration of aldehyde proton). [b] Decomposes in DMSO.

In the ^{13}C NMR spectra, containing both the formyl and methine carbons, there is the expected doubling of aromatic and methylene carbons, with a consistent pattern of intensities. It has even been possible to assign individual methylene carbons to the ring and chain tautomers by noting the parallel changes in intensities of families of carbons with solvent.[20]

We have measured the ring–chain equilibrium in three contrasting solvents by comparing the NMR proton integration of methine to that of formyl, according to eq 3.

$$K = \frac{\text{integration of methine proton}}{\text{integration of formyl proton}} = \frac{[\text{ring}]}{[\text{chain}]} \quad (3)$$

Methine and formyl protons were well-isolated from other resonances in all cases and so could be integrated with confidence. Integrations of remaining protons were internally consistent, with the exception of those from overlapping peaks, such as one aromatic proton in **3**[C] and the ethylenoxy region in that of **3** (see Experimental Section). The results are summarized in Table I.

For those compounds exhibiting ring–chain tautomerism, K varies as much as 10-fold for a single solvent (compare 3-phenyl **5** and 3-nitro **3** in chloroform). A

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(23) [R] and [C] represent the ring and chain tautomers, respectively, as shown in eq 1 and 2.

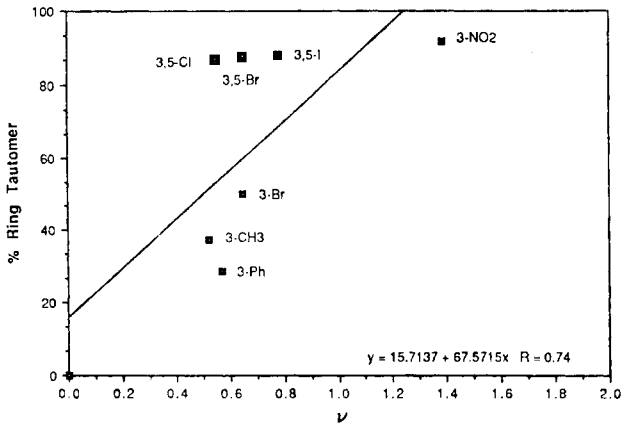

Figure 2. Plot of % ring tautomer vs ν of 3- and 3,5-substituted 2-(2-hydroxyethoxy)benzaldehydes in dimethyl-d_6 sulfoxide.

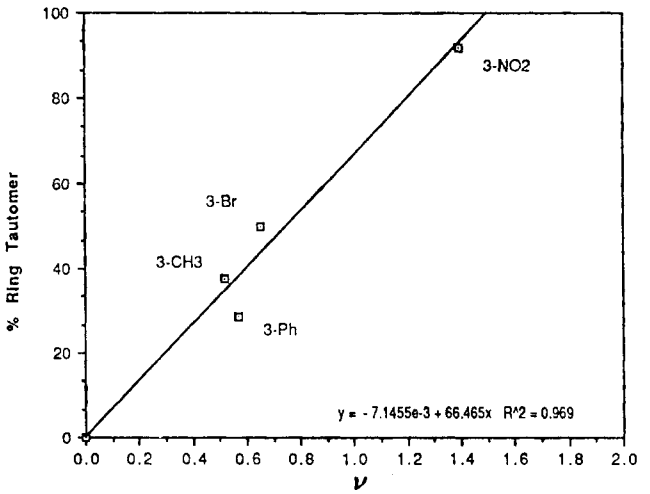

Figure 3. Plot of % ring tautomer vs ν of 3-substituted 2-(2-hydroxyethoxy)benzaldehydes in dimethyl-d_6 sulfoxide.

solvent change from chloroform to DMSO for an individual compound also increases K up to a factor of 10 (see 3-nitro **3** and 3,5-dichloro **10**). The broadest range of K's is 100-fold (compare 3-phenyl in chloroform and 3-nitro in DMSO).

The tendency for ring–chain tautomerism in this series is markedly dependent on the substituents. The ring tautomer is consistently present when an aromatic substituent is located in the 3-position (ortho to the alkoxy side chain). Thus, all 3- and 3,5-substituted compounds are ring–chain mixtures in solution, whereas the unsubstituted or 5-substituted compounds are exclusively chain.

A consideration of the role of the substituent can be approached by examining the trend within a given solvent. From this it is clear that the substituent is not exerting simply an electronic effect; if so, 3-bromo- and 5-bromo compounds should behave similarly, as should the 3-nitro and 5-nitro pair, for example. The broad scattering of points in a plot of percent ring tautomer versus either σ inductive[24] or σ meta[25,26] also confirms this conclusion. On the other hand, a plot of percent ring tautomer versus Charton's steric parameter ν[27] in all three solvents produces a reasonably good linear relationship in spite of some

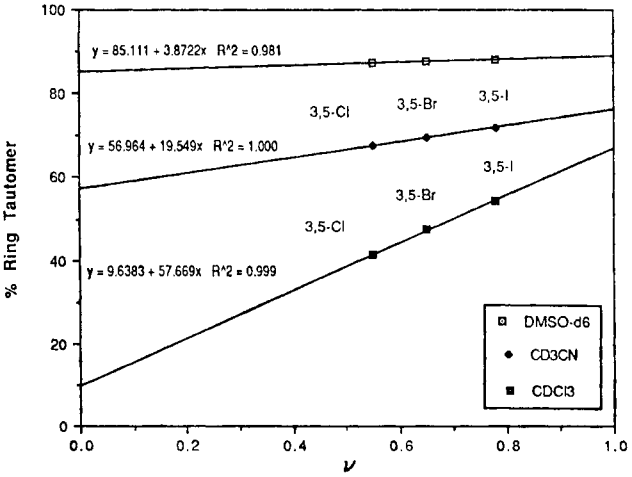

Figure 4. Plot of % ring tautomer vs ν of 3,5-disubstituted 2-(2-hydroxyethoxy)benzaldehydes.

scattering. This is illustrated in Figure 2 for the DMSO data. A t-test of the slopes[28] from separate plots of the 3- and 3,5-series justifies treating them as distinct data sets. When this was done, as shown in Figures 3 (DMSO) and 4 (all three solvents), the correlation coefficients (R) were all greater than 0.9. In the 3,5-series the slope is largest for chloroform and smallest for DMSO, a reflection of the strong effect of solvent on K. The correlation clearly shows that K increases in a linear fashion as the size of the 3-substituent becomes larger. This is the first instance in which an ortho steric effect has been noted for 7-membered tautomers. A steric bias toward ring tautomer in 5-membered rings, such as the lactol of *o*-acylbenzoic acids,[29,30] is well-known.

The effect of solvent on K appears to involve a delicate balance between the polar and hydrogen-bonding properties of the solvent with the ring and chain solutes. With the exception of the 3-bromo and 3-methyl compounds, a consistent trend is observed: a shift toward the ring tautomer with increasing solvent polarity. This can be noted from the change in K for a single compound in Table I. When the 3-substituent is electron-withdrawing, it is reasonable to expect that the ring tautomer, being more polar than the corresponding chain, would be favored as the solvent becomes more polar. However, when the 3-substituent is electron-donating as in the 3-methyl compound **6**, the more polar chain tautomer should be favored with increasing solvent polarity, as is the case. A 3-bromo substituent, intermediate in its electronic effect between methyl and nitro, seems to exert no stabilizing effect on either the ring or chain, for the K of **4** is insensitive to a change in solvent. This tentative explanation could be tested by examining a larger set of potential tautomers with a 3-substituent, but these would be derived from salicylaldehydes difficult to obtain.

The 3,5-dihalo compounds (**9**, **10**, **11**) show a significant increase in K as the solvent polarity increases (see Figure 4). This is interpreted as a *decrease* in the polarity of the *chain* tautomer, with its three complementary electron-withdrawing substituents in 1,3,5-positions. The net result is a widening of the difference in polarities between chain and ring, the latter being favored with an increase in solvent polarity. This is dramatically illustrated in the

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bromo series, where the second halogen exerts a synergistic effect by comparison with the 3-bromo compound, while the 5-bromo compound shows no tendency to cyclize in any solvent.

Hydrogen bonding of the ring or chain OH with solvent would be expected to be favored for the ring, with the more acidic OH, and to be enhanced, particularly in DMSO. (In a study of very similar compounds whose ring tautomers are 5- and 6-membered,[31] the pK_a's of the ring tautomer were determined to be about 12, whereas those of the chain are assumed to be greater than 14.) The fact that the NMR proton of the ring OH is downfield from that of the chain OH and is shifted further downfield as solvent polarity is increased is consistent with this superior H-bonding property of the ring over the chain. A rationalization of the solvent effect based on hydrogen bonding would fit all but the 3-bromo and 3-methyl compounds.

In conclusion, we have not found any tendency for 10-membered ring tautomer formation in the diethylenoxy series. In the ethylenoxy series the bias toward ring tautomer seems to be controlled primarily by the size of the 3-substituent. Secondary factors involving changes in polarity and hydrogen bonding with varying solvents can play a role in the position of the equilibrium. This study of a limited number of examples in one system involving 7-membered ring tautomers opens up the opportunity to explore these and other factors contributing to tautomeric behavior in a broad series of medium-size ring–chain pairs.

Experimental Section

General. Elemental analyses (CHN) on a Perkin-Elmer 240B were performed by Deanna Cardin at the University of New Hampshire. Bromine analyses were done by Galbraith Laboratories, Knoxville, TN. IR spectra were recorded on a Perkin-Elmer 283B grating spectrophotometer as a KBr pellet or neat film. ^{1}H NMR spectra were obtained from a Varian EM360A operating at 60 MHz, a JEOL FX90Q FTNMR operating at 90 MHz, or a Bruker AM360 operating at 360 MHz. ^{13}C NMR spectra were obtained from either a JEOL FX90Q FTNMR operating at 22.5 MHz or a Bruker AM360 operating at 90.56 MHz. Those spectra recorded on the JEOL are reported in ppm relative to TMS, the internal standard, unless specified otherwise, and those on the Bruker instrument are reported in ppm relative to the solvent chemical shift. The ^{1}H NMR spectra of substituted 2-(2-hydroxyethoxy)benzaldehydes (0.029–0.059 M) were recorded shortly after sample preparation, and no change had occurred after 24 h, with the exception of **2** in DMSO. A detailed statistical analysis of K for each ethylenoxy compound was not done, but K for the dichloro compound was determined to be ±0.02. The deviation in K for the other compounds is presumed to differ at most by ±0.1. Low-resolution MS were performed by William Dotchin at the University of New Hampshire on either a Hitachi Perkin-Elmer Model RMU-6E or a Hewlett Packard 5988A. High resolution mass spectra (HRMS) were done by Midwest Center for Mass Spectrometry in Lincoln, NE. All reactions were conducted under a nitrogen atmosphere.

General Procedure for the Preparation of Substituted 2-(2-Hydroxyethoxy)benzaldehydes. A solution of the sodium salt of the salicylaldehyde (0.2–3.0 g) and 2-bromoethanol (2.5 equiv) in 25 mL of prepurified DMF was stirred at room temperature for 6 h to 26 days and monitored by TLC until all the sodium salt had been consumed. The reaction mixture was poured into 200–300 mL of chilled 5% aqueous sodium hydroxide. The aqueous solution was extracted with 4 × 60 mL of methylene chloride. The combined extracts were washed with water (50–100 mL), dried with magnesium sulfate, and concentrated under reduced pressure to afford the crude benzaldehydes. Purification was accomplished by recrystallization or preparative TLC.

2-(2-Hydroxyethoxy)benzaldehyde (2): yellow oil; ^{1}H NMR ($CDCl_3$, 60 MHz) 10.5 (s, 1 H, CHO), 8.0–6.85 (m, 4 H, ArH), 4.5–3.5 (m, 4 H, OCH_2CH_2O), 3.2 (br s, 1 H, OH); ^{1}H NMR (CD_3CN, 360 MHz) 10.50 (s, 0.7 H, CHO), 7.74 (m, 1.0 H, Ar H), 7.59 (m, 1.0 H, Ar H), 7.02–7.13 (m, 2.1 H, Ar H), 4.1 (m, 2.4 H, CH_2), 3.8 (m, 2.1 H, CH_2), 2.4 (br s, 1.5 H, OH and water).

Semicarbazone: mp 169–171 °C (ethanol–water). Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.54; H, 4.95; N, 18.89.

3-Nitro-2-(2-hydroxyethoxy)benzaldehyde (3): yellow solid; mp 88–89 °C (ethanol–water); ^{1}H NMR ($CDCl_3$, 360 MHz) 10.42 (s, 1.0 H, CHO), 8.09 (d, J = 7.9 Hz, 2.0 H, Ar H [C]), 7.74 (dd, J = 7.9, 1.7 Hz, 1.6 H, Ar H [R]), 7.68 (dd, J = 7.9, 1.7 Hz, 1.8 H, Ar H [R]), 7.38 (t, J = 7.9 Hz, 1.0 H, Ar H [C]), 7.19 (t, J = 7.9 Hz, 2.0 H, Ar H [R] and $CHCl_3$), 5.96 (d, J = 4.6 Hz, 1.6 H, OCHO), 4.34–3.98 (m, 12.0 H, OCH_2CH_2O [R] and [C]), 3.23 (d, J = 4.6 Hz, 1.6 H, OH [R]), 2.28 (t, J = 5.7 Hz, 1.0 H, OH [C]); ^{1}H NMR (CD_3CN, 360 MHz), 10.44 (s, 1.0 H, CHO), 8.11 (dd, J = 8.0, 1.8 Hz, 1.0 H, Ar H [C]), 8.06 (dd, J = 8.0, 1.8 Hz, 1.0 H, Ar H [C]), 7.70 (dd, J = 7.9, 1.7 Hz, 3.0 H, Ar H [R]), 7.66 (dd, J = 7.9, 1.7 Hz, 3.0 H, Ar H [R]), 7.41 (t, J = 8.0 Hz, 1.0 H, Ar H [C]), 7.21 (t, J = 7.9 Hz, 3.0 H, Ar H [R]), 5.88 (s, 2.9 H, OCHO), 5.14 (br s, 2.5 H, OH [R]), 4.28–3.80 (m, 17.0 H, OCH_2CH_2O [R] and [C]), 3.11 (br s, 1.0 H, OH [C]); ^{1}H NMR (DMSO-d_6, 360 MHz) 10.42 (s, 1.0 H, CHO), 8.24 (dd, J = 7.9, 1.7 Hz, 1.0 H, Ar H [C]), 8.04 (dd, J = 7.9, 1.7 Hz, 1.1 H, Ar H [C]), 7.75 (dd, J = 8.0, 1.6 Hz, 10.3 H, Ar H [R]), 7.69 (dd, J = 8.0, 1.6 Hz, 11.7 H, Ar H [R]), 7.48 (t, J = 7.9 Hz, 1.9 H, Ar H [C]), 7.41 (d, J = 5.0 Hz, 10.4 H, OH [R]), 7.25 (t, J = 8.0 Hz, 11.7 H, Ar H [R]), 5.85 (d, J = 5.0 Hz, 11.4 H, OCHO), 4.97 (t, J = 5.0 Hz, 1.2 H, OH [C]), 4.27–3.70 (m, 60.25 H, OCH_2CH_2O [R] and [C]); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 188.16, 154.67, 150.42, 143.60, 136.89, 134.50, 131.31, 130.86, 130.83, 124.50, 124.39, 123.57, 96.11, 79.51, 73.63, 67.46, 61.79; ^{13}C NMR (CD_3CN, 90.56 MHz) 189.66, 150.94, 138.50, 134.0, 131.67, 131.65, 125.38, 124.61, 124.27, 96.34, 80.24, 74.75, 67.38, 61.74; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 188.95, 154.41, 149.39, 143.33, 137.55, 132.86, 131.09, 130.81, 128.89, 128.20, 124.65, 123.47, 123.29, 95.16, 79.45, 73.72, 65.70, 60.19; MS m/z 211 (M^+). HRMS: Calcd for $C_9H_9NO_5$, 211.0481. Found (m/z) 211.0481.

3-Bromo-2-(2-hydroxyethoxy)benzaldehyde (4): yellow solid; mp 122–126 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) 10.40 (d, J = 0.78 Hz, 1 H, CHO), 7.78 (m, 2 H, Ar H [C] and [R]), 7.49 (dd, J = 7.9 , 1.6 Hz, 1 H, Ar H [C]), 7.31 (m, 1 H, Ar H [R]), 7.11 (m, 1 H, Ar H [C]), 6.93 (t, J = 7.9 Hz, 1 H, Ar H [R]), 5.64 (s, 1 H, OCHO), 4.4–4.01 (m, 8 H, OCH_2CH_2O [R] and [C]), 1.52 (s, H_2O and OH [R] and [C]); ^{1}H NMR (CD_3CN, 360 MHz) 10.34 (d, J = 0.77 Hz, 1 H, CHO), 7.86 (dd, J = 7.9, 1.7 Hz, 1 H, Ar H [C]), 7.73 (dd, J = 7.7, 1.6 Hz, 1 H, Ar H [R]), 7.53 (dd, J = 7.9, 1.7 Hz, 1 H, Ar H [C]), 7.29 (ddd, J = 7.7, 1.6, 0.5 Hz, 1 H, Ar H [R]), 7.18 (td, J = 7.9, 0.77 Hz, 1 H, Ar H [C]), 6.95 (t, J = 7.7 Hz, 1 H, Ar H [R]), 5.65 (s, 1 H, OCHO), 4.40–3.97 (m, 4 H, OCH_2CH_2O [C] and [R]), 2.24 (br s, H_2O and OH [R] and [C]); ^{1}H NMR (DMSO-d_6, 360 MHz) 10.28 (s, 1 H, CHO), 7.96 (dd, J = 7.9, 1.6 Hz, 1 H, Ar H [C]), 7.70 (dd, J = 7.8, 1.6 Hz, 1 H, Ar H [R]), 7.56 (dd, J = 7.9, 1.6 Hz, 1 H, Ar H [C]), 7.29–7.23 (m, 2 H, Ar H [R] and [C]), 6.97 (t, J = 7.8 Hz, 1 H, Ar H [R]), 5.71 (s, 1 H, OCHO), 4.38–3.99 (m, 4 H, OCH_2CH_2O [C] and [R]), 3.34 (br s, H_2O and OH [R] and [C]; ^{13}C NMR ($CDCl_3$, 90.56 MHz) 189.39, 139.39, 133.21, 127.85, 126.60, 125.81, 124.45, 115.86, 102.19, 77.76, 74.79, 72.77, 67.43; ^{13}C NMR (CD_3CN, 90.56 MHz) 190.40, 159.58, 140.20, 135.16, 133.84, 132.09, 128.47, 127.90, 126.83, 125.16, 116.11, 102.63, 75.70, 73.71, 68.13, 67.29; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 189.55, 139.38, 132.84, 127.71, 127.22, 126.21, 124.26, 101.09, 74.72, 72.69, 66.96, 65.89; MS m/z 246, 244 (M^+). HRMS: Calcd for $C_9H_9BrO_3$, 243.9735. Found (m/z) 243.9741.

3-Phenyl-2-(2-hydroxyethoxy)benzaldehyde (5): yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz, TMS reference) 10.41 (s, 1.0 H, CHO), 7.83 (dd, J = 7.6, 1.7 Hz, 1.0 H, Ar H [C]), 7.61 (dd, J = 7.6, 1.7 Hz, 1.0 H, Ar H [C]), 7.57–7.38 (m, 5.5 H, Ar H [C] and [R]), 7.33 (t, J = 7.6 Hz, 1.0 H, Ar H [C]), 7.15 (t, J = 7.6 Hz, 0.1 H, Ar H [R]), 5.97 (s, 0.1 H, OCHO), 4.26–3.99 (m, 0.4 H, OCH_2CH_2O [R]), 3.72–3.61 (m, 4.0 H, OCH_2CH_2O [C]), 2.41 (br s, 1.0 H, OH [C]), 1.81 (br s, 0.1 H, OH [R]); ^{1}H NMR (CD_3CN, 360 MHz) 10.50 (s, 1.0 H, CHO), 7.78 (dd, J = 7.7, 1.7 Hz, 1.0 H, Ar H [C]), 7.65–7.11 (m, 10.2 H, Ar H [C] and [R]), 5.87 (br s, 0.24 H, OCHO), 4.88 (br s, 0.3 H, OH [R]), 4.17–3.81 (m, 1.4 H, OCH_2CH_2O [R]), 3.61–3.4 (m, 4.4 H, OCH_2CH_2O [C]), 2.86 (m, 1.0 H, OH [C]); ^{1}H

(31) Harron, J.; McClelland, R. A.; Thankachan, C.; Tidwell, T. T. *J. Org. Chem.* **1981**, *46*, 903–910.

NMR (DMSO-d_6, 360 MHz) 10.48 (s, 1.0 H, CHO), 7.72 (dd, J = 7.7, 1.7 Hz, 1.0 H, Ar H [C]), 7.65 (dd, J = 7.7, 1.7 Hz, 1.0 H, Ar H [C]), 7.56–7.22 (m, 9.0 H, Ar H [C] and [R]), 7.12 (t, J = 7.6 Hz, 0.4 H, Ar H [R]), 5.78 (s, 0.4 H, OCHO), 4.10–3.76 (m, 1.7 H, OCH_2CH_2O [R]), 3.63–3.61 (br s, H_2O and OH [C] and [R]), 3.54–3.40 (m, 4.0 H, OCH_2CH_2O [C]); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 190.83, 158.59, 154.34, 138.01, 137.29, 137.04, 136.29, 134.39, 134.30, 130.90, 129.71, 129.58, 129.36, 129.01, 128.85, 128.75, 128.63, 128.46, 128.15, 127.98, 127.01, 126.34, 124.61, 123.63, 96.93, 76.67, 72.95, 66.64, 61.43; ^{13}C NMR (CD_3CN, 90.56 MHz) 191.67, 160.39, 155.55, 139.31, 138.18, 138.11, 136.93, 136.35, 134.94, 131.30, 130.91, 130.27, 129.88, 129.49, 129.45, 128.91, 128.69, 128.21, 127.88, 127.21, 125.42, 124.21, 97.04, 77.25, 73.87, 67.47, 61.50; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 191.27, 159.68, 154.62, 138.32, 137.59, 137.10, 135.91, 135.71, 133.73, 130.35, 129.87, 129.50, 128.99, 128.95, 128.38, 128.16, 127.24, 127.00, 126.70, 124.97, 123.48, 95.89, 76.50, 73.04, 66.57, 60.00; MS m/z 242 (M^+). HRMS: Calcd for $C_{15}H_{14}O_3$, 242.0943. Found (m/z) 242.0938.

3-Methyl-2-(2-hydroxyethoxy)benzaldehyde (6): white solid; mp 75–78 °C; ^1H NMR ($CDCl_3$, 360 MHz) 10.41 (s, 1.0 H, CHO), 7.66 (d, J = 7.7 Hz, 1.1 H, Ar H [C]), 7.41 (m, 1.2 H, Ar H [C]), 7.24–7.20 (m, Ar H [R] and $CHCl_3$), 7.14–7.10 (m, 2.1 H, Ar H [R] and [C]), 6.94 (t, J = 7.6 Hz, 1.1 H, Ar H [R]), 5.64 (s, 1.0 H, OCHO), 4.27–3.94 (m, 8.9 H, OCH_2CH_2O [R] and [C]), 2.33 (s, 3.2 H, CH_3 [C]), 2.24 (s, 3.2 H, CH_3 [R]), 1.5 (s, H_2O and OH [R] and [C]); ^1H NMR (DMSO-d_6, 360 MHz) 10.38 (s, 1.0 H, CHO), 7.57–7.53 (m, 2.1 H, Ar H [C]), 7.22–7.08 (m, 2.3 H, Ar H [R] and [C]), 6.91 (t, J = 7.5 Hz, 0.6 H, Ar H [R]), 5.72 (s, 0.6 H, OCHO), 4.13–3.69 (m, 9.0 H, H_2O and OCH_2CH_2O, OH [R] and [C]), 2.30 (s, 3.8 H, CH_3 [C]), 2.12 (s, 1.7 H, CH_3 [R]); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 190.59, 160.29, 155.68, 137.54, 132.37, 131.78, 131.02, 129.82, 129.34, 126.52, 125.17, 124.39, 122.94, 102.94, 74.70, 72.18, 67.35, 67.16, 16.14, 15.82; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 190.98, 160.48, 155.68, 137.71, 134.54, 132.46, 130.20, 129.06, 128.99, 125.52, 124.74, 124.30, 122.49, 95.76, 77.35, 72.03, 66.40, 60.25, 16.04, 15.54; MS m/z 180 (M^+).

Semicarbazone: mp 186–189 °C (ethanol–water). Anal. Calcd for $C_{11}H_{15}N_3O_3$ (237): C, 55.69; H, 6.37; N, 17.71. Found: C, 55.82; H, 6.53; N, 17.78.

5-Nitro-2-(2-hydroxyethoxy)benzaldehyde (7): white solid; mp 76–78 °C (chloroform–hexane); ^1H NMR ($CDCl_3$, 360 MHz) 10.45 (s, 1 H, CHO), 8.69 (d, J = 2.9 Hz, 1 H, Ar H), 8.42 (dd, J = 9.2, 2.9 Hz, 1 H, Ar H), 7.13 (d, J = 9.2 Hz, 1 H, Ar H), 4.35–4.32 (m, 2 H, $ArOCH_2$), 4.12–4.07 (m, 2 H, CH_2O), 2.04 (t, J = 5.8 Hz, 1 H, OH); ^1H NMR (CD_3CN, 360 MHz) 10.47 (s, 1 H, CHO), 8.50 (d, J = 2.9 Hz, 1 H, Ar H), 8.42 (dd, J = 9.2, 2.9 Hz, 1 H, Ar H), 7.30 (d, J = 9.2 Hz, 1 H, Ar H), 4.31–4.28 (m, 2 H, $ArOCH_2$), 3.92–3.87 (m, 2 H, CH_2O), 3.34 (br s, 1 H, OH); ^1H NMR (DMSO-d_6, 360 MHz) 10.41 (s, 1 H, CHO), 8.47 (dd, J = 9.2, 2.9 Hz, 1 H, Ar H), 8.39 (d, J = 2.9 Hz, 1 H, Ar H), 7.47 (d, J = 9.2 Hz, 1 H, Ar H), 5.07 (t, J = 5.9 Hz, 1 H, OH), 4.32–4.29 (m, 2 H, $ArOCH_2$), 3.82–3.78 (m, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 187.34, 164.64, 141.82, 130.63, 125.29, 124.78, 113.20, 70.99, 60.90; ^{13}C NMR (CD_3CN, 90.56 MHz) 189.13, 166.33, 142.29, 131.51, 125.43, 124.33, 115.05, 72.56, 60.71; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 188.51, 165.30, 140.74, 130.90, 124.03, 123.07, 114.87, 71.85, 59.23; MS m/z 211 (M^+).

Anal. Calcd for $C_9H_9NO_5$ (211): C, 51.19; H, 4.30; N, 6.63. Found: C, 50.88; H, 4.27; N, 6.54.

5-Bromo-2-(2-hydroxyethoxy)benzaldehyde (8): white solid; mp 80–81 °C (hexane); ^1H NMR ($CDCl_3$, 360 MHz) 10.38 (s, 1 H, CHO), 7.91 (d, J = 2.6 Hz, 1 H, Ar H), 7.62 (dd, J = 8.9, 2.6 Hz, 1 H, Ar H), 6.90 (d, J = 8.9 Hz, 1 H, Ar H), 4.2–4.17 (m, 2 H, $ArOCH_2$), 4.05–4.0 (m, 2 H, CH_2O), 2.01 (t, J = 6.0 Hz, OH); ^1H NMR (CD_3CN, 360 MHz) 10.41 (s, 1 H, CHO), 7.81 (d, J = 2.6 Hz, 1 H, Ar H), 7.69 (dd, J = 8.9, 2.6 Hz, 1 H, Ar H), 7.08 (d, J = 8.9 Hz, 1 H, Ar H), 4.16–4.13 (m, 2 H, $ArOCH_2$), 3.86–3.83 (m, 2 H, CH_2O), 2.15 (br s, H_2O and OH [R] and [C]); ^1H NMR (DMSO-d_6, 360 MHz) 10.36 (s, 1 H, CHO), 7.78 (dd, J = 8.9, 2.6 Hz, 1 H, Ar H), 7.71 (d, J = 2.6 Hz, 1 H, Ar H), 7.23 (d, J = 8.9 Hz, 1 H, Ar H), 4.98 (t, J = 5.8 Hz, 1 H, OH), 4.16–4.13 (m, 2 H, $ArOCH_2$), 3.77–3.73 (m, 2 H, CH_2O); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 188.10, 159.77, 138.31, 131.81, 126.39, 114.98, 114.00, 70.45, 61.15; ^{13}C NMR (CD_3CN, 90.56 MHz) 189.36, 161.45, 139.15, 130.87, 127.31, 116.86, 113.69, 71.89, 60.92; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 188.66, 160.32, 138.45, 129.43, 125.90, 116.64, 112.44, 71.06, 59.37; MS m/z 246, 244 (M^+).

Anal. Calcd for $C_9H_9BrO_3$ (245): C, 44.26; H, 3.69. Found: C, 44.28; H, 3.82.

3,5-Dibromo-2-(2-hydroxyethoxy)benzaldehyde (9): white solid; mp 144–145 °C (ethanol); ^1H NMR ($CDCl_3$, 360 MHz) 10.27 (s, 1.0 H, CHO), 7.92 (d, J = 2.5 Hz, 1.0 H, Ar H [C]), 7.88 (d, J = 2.5 Hz, 1.0 H, Ar H [C]), 7.63 (d, J = 2.3 Hz, 0.9 H, Ar H [R]), 7.58 (d, J = 2.3 Hz, 0.9 H, Ar H [R]), 5.86 (d, J = 4.7 Hz, 0.9 H, OCHO), 4.28–3.89 (m, 9 H, OCH_2CH_2O [C] and [R]), 3.13 (d, J = 4.7 Hz, 0.9 H, OH [R]), 2.26 (t, J = 5.9 Hz, 1.0 H, OH [C]); ^1H NMR (CD_3CN, 360 MHz) 10.31 (s, 1.0 H, CHO), 8.04 (d, J = 2.4 Hz, 1.0 H, Ar H [C]), 7.85 (d, J = 2.4 Hz, 1.0 H, Ar H [C]), 7.70 (d, J = 2.5 Hz, 2.2 H, Ar H [R]), 7.56 (dd, J = 2.5, 0.6 Hz, 2.3 H, Ar H [R]), 5.78 (m, 2.3 H, OCHO), 5.26 (d, J = 4.4 Hz, 2.0 H, OH [R]), 4.23–3.83 (m, 13.5 H, OCH_2CH_2O [C] and [R]), 3.23 (t, J = 5.6 Hz, 0.7 H, OH [C]); ^1H NMR (DMSO-d_6, 360 MHz) 10.29 (s, 1.0 H, CHO), 8.22 (d, J = 2.5 Hz, 1.0 H, Ar H [C]), 7.93–7.77 (m, 7.5 H, Ar H [C] and [R]), 7.54 (d, J = 2.4 Hz, 7.1 H, Ar H [R]), 7.40 (d, J = 5.0 Hz, 7.1 H, OH [R]), 5.76 (d, J = 5.0 Hz, 7.1 H, OCHO), 4.99 (t, J = 5.1 Hz, 0.9 H, OH [C]), 4.35–3.72 (m, 37 H, OCH_2CH_2O [C] and [R]); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 187.98, 157.46, 153.50, 141.32, 136.62, 135.21, 131.75, 131.67, 129.18, 119.33, 118.25, 116.91, 116.53, 95.82, 77.52, 72.91, 67.55, 61.80; ^{13}C NMR (CD_3CN, 90.56 MHz) 189.47, 159.17, 154.71, 141.79, 138.92, 135.29, 133.01, 131.00, 129.93, 120.03, 117.34, 116.30, 95.86, 78.44, 73.80, 67.73, 61.61; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 157.99, 153.46, 140.67, 138.25, 133.94, 129.72, 129.33, 117.20, 116.30, 115.06, 94.68, 77.54, 72.88, 66.11, 60.09; MS m/z 326, 324, 322 (M^+).

Anal. Calcd for $C_9H_8Br_2O_3$ (324): C, 33.33; H, 2.47. Found: C, 33.63; H, 2.56.

3,5-Dichloro-2-(2-hydroxyethoxy)benzaldehyde (10): white solid; mp 127–128 °C (ethanol–water, lit.[16] mp 127–129 °C); ^1H NMR ($CDCl_3$), 360 MHz) 10.29 (s, 1.0 H, CHO), 7.69 (d, J = 2.5 Hz, 1.0 H, Ar H [C]), 7.61 (d, J = 2.5 Hz, 1.0 H, Ar H [C]), 7.40 (d, J = 2.5 Hz, 0.7 H, Ar H [R]), 7.33 (d, J = 2.5 Hz, 0.7 H, Ar H [R]), 5.86 (s, 0.7 H, OCHO), 4.28–3.90 (m, 8.2 H, OCH_2CH_2O [C] and [R]), 3.34 (br s, 0.8 H, OH [R]), 2.35 (br s, 1.0 H, OH [C]); ^1H NMR (CD_3CN, 360 MHz) 10.35 (s, 1.0 H, CHO), 7.76 (d, J = 2.6 Hz, 1.1 H, Ar H [C]), 7.68 (d, J = 2.6 Hz, 1.1 H, Ar H [C]), 7.41 (d, J = 2.5 Hz, 2.1 H, Ar H [R]), 7.38 (d, J = 2.5 Hz, 2.1 H, Ar H [R]), 5.79 (d, J = 5.0 Hz, 2.1 H, OCHO), 5.26 (d, J = 5.0 Hz, 1.9 H, OH [R]), 4.25–3.80 (m, 14.8 H, OCH_2CH_2O [C] and [R]), 3.21 (t, J = 5.5 Hz, 1.0 H, OH [C]); ^1H NMR (DMSO-d_6, 360 MHz) 10.33 (s, 1.0 H, CHO), 8.01 (d, J = 2.63 Hz, 1.0 H, Ar H [C]), 7.63 (d, J = 2.63 Hz, 1.0 H, Ar H [C]), 7.55 (d, J = 2.58 Hz, 5.3 H, Ar H [R]), 7.41 (d, J = 5.0 Hz, 6.5 H, OH [C]), 7.39 (d, J = 2.58 Hz, 6.5 H, Ar H [R]), 5.77 (d, J = 5.0 Hz, 6.8 H, OCHO), 4.97 (t, J = 5.2 Hz, 1.1 H, OH [C]), 4.26–3.70 (m, 34.0 H, OCH_2CH_2O [R] and [C]); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 188.17, 155.93, 151.99, 136.47, 135.71, 131.27, 130.60, 129.82, 129.62, 128.85, 127.95, 127.24, 124.49, 95.88, 77.21, 73.05, 67.61, 61.76; ^{13}C NMR (CD_3CN, 90.56 MHz) 189.51, 157.69, 153.24, 138.79, 136.19, 132.67, 130.57, 129.73, 128.68, 127.64, 127.15, 126.28, 95.96, 78.17, 73.96, 67.78, 61.62; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 188.76, 156.53, 152.03, 138.09, 135.23, 131.52, 129.30, 129.06, 128.55, 126.94, 126.13, 126.00, 125.78, 94.76, 77.32, 73.03, 66.12, 60.11; MS m/z 238, 236, 234 (M^+).

3,5-Diiodo-2-(2-hydroxyethoxy)benzaldehyde (11): tan-white solid; mp 140–142 °C (ethanol); ^1H NMR ($CDCl_3$, 360 MHz) 10.18 (s, 1.0 H, CHO), 8.31 (d, J = 2.1 Hz, 1.0 H, Ar H [C]), 8.07 (d, J = 2.1 Hz, 1.0 H, Ar H [C]), 8.01 (d, J = 2.0 Hz, 1.2 H, Ar H [R]), 7.76 (d, J = 2.0 Hz, 1.2 H, Ar H [R]), 5.82 (d, J = 5.0 Hz, 1.2 H, OCHO), 4.25–3.87 (m, 9 H, OCH_2CH_2O [C] and [R]), 3.17 (d, J = 5.0 Hz, 1.1 H, OH [R]), 2.29 (m, 1.0 H, OH [C]); ^1H NMR (CD_3CN, 360 MHz) 10.23 (s, 1.0 H, CHO), 8.41 (d, J = 1.9 Hz, 1.0 H, Ar H [C]), 8.06 (d, J = 1.8 Hz, 2.6 H, Ar H [R]), 8.03 (d, J = 1.9 Hz, 1.0 H, Ar H [C]), 7.73 (d, J = 1.8 Hz, 2.7 H, Ar H [R]), 5.74 (d, J = 4.5 Hz, 2.6 H, OCHO), 5.19 (d, J = 4.5 Hz, 2.2 H, OH [R]), 4.20–3.79 (m, 18.5 H, OCH_2CH_2O [C] and [R]), 3.22 (t, J = 5.5 Hz, 1.2 H, OH [C]); ^1H NMR (DMSO-d_6, 360 MHz) 10.22 (s, 1.0 H, CHO), 8.43 (d, J = 2.1 Hz, 0.9 H, Ar H [C]), 8.00 (d, J = 2.0 Hz, 7.0 H, Ar H [R]), 7.92 (d, J = 2.1 Hz, 1.0 H, Ar H [C]), 7.69 (d, J = 2.0 Hz, 7.2 H, Ar H [R]), 7.32 (d, J = 5.0 Hz, 7.3 H, OH [R]), 5.70 (d, J = 5.0 Hz, 7.4 H, OCHO), 5.00 (t, J = 5.2 Hz, 0.8 H, OH [C]), 4.20–3.74 (m, 35.6 H, OCH_2CH_2O [C] and [R]); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 188.05, 160.59, 156.66, 152.55,

146.38, 139.02, 136.14, 135.86, 131.21, 95.61, 94.64, 92.53, 89.31, 87.69, 77.96, 72.76, 67.36, 61.83; ^{13}C NMR (CD_3CN, 90.56 MHz) 189.62, 162.39, 157.89, 153.17, 146.60, 138.32, 138.05, 136.98, 132.50, 95.70, 93.10, 89.40, 87.48, 78.92, 73.64, 67.60, 61.63; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 189.13, 156.55, 155.82, 151.73, 144.90, 137.36, 136.51, 135.93, 131.32, 96.35, 94.53, 93.61, 90.35, 87.99, 77.87, 72.59, 66.09, 60.05; MS m/z 418 (M^+).

Anal. Calcd for $C_9H_8I_2O_3$ (418): C, 25.84; H, 1.91. Found: C, 25.81; H, 2.10.

General Procedure for the Preparation of Substituted 2-(5-Hydroxy-3-oxapentyloxy)benzaldehydes. A solution of the sodium salt of the salicylaldehyde (0.5–1.0 g), sodium iodide (0.1 equiv), and 2-(2-chloroethoxy)ethanol (2 equiv) in 15–20 mL of prepurified DMF was stirred at reflux for 1.5–6 h until no more solid appeared to have precipitated. The supernatant was decanted, and the solid was washed with ethyl acetate. The combined solutions were concentrated under reduced pressure. The residue was taken up in ethyl acetate; the mixture was filtered and the filtrate concentrated under reduced pressure to afford a mixture of *o*-hydroxyalkoxybenzaldehyde and recovered salicylaldehyde. Purification of the benzaldehydes was accomplished by column, flash, or preparative TLC.

3-Nitro-2-(5-hydroxy-3-oxapentyloxy)benzaldehyde (12): orange oil; ^{1}H NMR ($CDCl_3$, 90 MHz) 10.49 (d, J = 0.8 Hz, 1 H, CHO), 8.1 (m, 2 H, Ar H), 7.37 (m, 1 H, Ar H), 4.5–4.3 (m, 2 H, $ArOCH_2$), 3.9–3.4 (m, 6 H, $CH_2OCH_2CH_2O$), 2.3 (br s, 1 H, OH); ^{1}H NMR (DMSO-d_6, 90 MHz) 10.36 (s, 1 H, CHO), 8.31–8.01 (m, 2 H, Ar H), 7.58–7.40 (m, 1 H, Ar H), 4.33–4.23 (m, 2 H, $ArOCH_2$), 3.78–3.36 (m, $CH_2OCH_2CH_2OH$, H_2O); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 188.6, 155.2, 133.4, 131.8, 130.7, 124.4, 72.7, 70.1, 61.7.

Semicarbazone: mp 135–136 °C (ethanol–water). Anal. Calcd for $C_{12}H_{16}N_4O_6$ (312): C, 46.16; H, 5.16; N, 17.94. Found: C, 46.03; H, 5.27; N, 17.75.

3-Phenyl-2-(5-hydroxy-3-oxapentyloxy)benzaldehyde (13): yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz) 10.56 (s, 1 H, CHO), 7.84 (dd, J = 7.7, 1.6 Hz, 1 H, Ar H), 7.7–7.25 (m, 7 H, Ar H), 3.77–3.44 (m, 8 H, $OCH_2CH_2OCH_2CH_2O$), 2.08 (v br s, 1 H, OH); ^{1}H NMR (DMSO-d_6, 360 MHz) 10.42 (s, 1 H, CHO), 7.72 (d, J = 7.5 Hz, 1 H, Ar H), 7.66 (d, J = 7.5 Hz, 1 H, Ar H), 7.62–7.22 (m, 6 H, Ar H), 3.6 (s, OH and H_2O), 3.5–3.19 (m, 8 H, $OCH_2CH_2OCH_2CH_2O$); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 191.17, 159.48, 137.25, 137.17, 135.89, 130.06, 129.01, 128.57, 127.84, 127.39, 124.59, 73.62, 72.29, 69.84, 61.69; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 191.12, 159.42, 137.57, 137.07, 135.67, 129.93, 129.01, 128.97, 128.17, 127.02, 125.04, 73.79, 72.15, 69.27, 60.17; MS m/z 286 (M^+).

Semicarbazone: mp 148–149 °C (ethanol–water). Anal. Calcd for $C_{18}H_{21}N_3O_4$ (343): C, 62.96; H, 6.17; N, 12.24. Found: C, 63.09; H, 6.27; N, 11.93.

5-Bromo-2-(5-hydroxy-3-oxapentyloxy)benzaldehyde (14): white solid; mp 55–56 °C (ethyl acetate/cyclohexane); ^{1}H NMR ($CDCl_3$, 90 MHz) 10.4 (s, 1 H, CHO), 7.91 (d, J = 2.6 Hz, 1 H, ArH), 7.61 (dd, J = 8.8, 2.6 Hz, 1 H, Ar H), 6.90 (d, J = 8.8 Hz, 1 H, Ar H), 4.3–4.15 (m, 2 H, $ArOCH_2$), 4.01–3.59 (m, 6 H, $CH_2OCH_2CH_2O$), 2.11 (br s, 1 H, OH); ^{1}H NMR (DMSO-d_6, 90 MHz) 10.30 (s, 1 H, CHO), 7.87–7.71 (m, 2 H, Ar H), 7.25 (d, J = 8.5 Hz, 1 H, Ar H), 4.63–4.23 (m, 2 H, $ArOCH_2$), 3.86–3.76 (m, 2 H, CH_2O), 3.6–3.3 (m, 4 H, OCH_2CH_2O); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 188.2, 160.0, 138.2, 131.2, 126.6, 114.9, 113.9, 72.8, 69.4, 68.7, 61.8; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 188.35, 160.18, 138.59, 129.73, 126.01, 116.90, 112.73, 72.54, 68.95, 68.67, 60.23; MS m/z 290, 288 (M^+).

Anal. Calcd for $C_{11}H_{13}BrO_4$ (289): C, 45.67; H, 4.50; Br, 27.68. Found: C, 45.78; H, 4.77; Br, 27.39.

3,5-Dibromo-2-(5-hydroxy-3-oxapentyloxy)benzaldehyde (15): yellow oil; ^{1}H NMR ($CDCl_3$, 90 MHz) 10.36 (s, 1 H, CHO), 7.92 (d, J = 2.6 Hz, 1 H, Ar H), 7.89 (d, J = 2.6 Hz, 1 H, Ar H), 4.36–4.15 (m, 2 H, $ArOCH_2$), 3.90–3.54 (m, 6 H, $CH_2OCH_2CH_2O$), 2.04 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 188.6, 158.1, 141.2, 132.1, 130.5, 119.0, 118.2, 74.9, 72.7, 70.0, 61.8; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 189.04, 157.98, 140.89, 132.17, 130.07, 119.46, 117.52, 75.07, 72.33, 69.53, 60.19; MS m/z 370, 368, 366 (M^+).

Semicarbazone: mp 175–176 °C (ethanol–water). Anal. Calcd for $C_{12}H_{15}Br_2N_3O_4$ (425): C, 33.88; H, 3.52; N, 9.88; Br, 37.65. Found: C, 34.28; H, 3.70; N, 9.84; Br, 37.45.

3,5-Dichloro-2-(5-hydroxy-3-oxapentyloxy)benzaldehyde (16): yellow oil; ^{1}H NMR ($CDCl_3$, 60 MHz) 10.45 (s, 1 H, CHO), 7.7 (d, J = 2.5 Hz, 1 H, Ar H), 7.6 (d, J = 2.5 Hz, 1 H, Ar H), 4.5–4.2 (m, 2 H, $ArOCH_2$), 4.0–3.5 (m, 6 H, $CH_2OCH_2CH_2O$), 2.75 (br s, 1 H, OH); ^{1}H NMR (DMSO-d_6, 60 MHz) 10.3 (s, 1 H, CHO), 8.0 (d, J = 2 Hz, 1 H, Ar H), 7.65 (d, J = 2 Hz, 1 H, Ar H), 4.45–4.1 (m, 2 H, $ArOCH_2$), 3.9–3.2 (m, $CH_2OCH_2CH_2OH$ and H_2O); ^{13}C NMR ($CDCl_3$, 22.5 MHz) 188.6, 156.5, 135.5, 131.8, 130.5, 129.6, 126.6, 74.7, 72.6, 70.0, 61.8; ^{13}C NMR (DMSO-d_6, 22.5 MHz, DMSO reference) 188.5, 156.2, 135.0, 131.5, 129.2, 129.1, 126.1, 74.6, 72.1, 69.2, 60.0; MS m/z 280, 278 (M^+).

Anal. Calcd for $C_{11}H_{12}Cl_2O_4$ (279): C, 47.33; H, 4.34. Found: C, 47.44; H, 4.54.

3,5-Diiodo-2-(5-hydroxy-3-oxapentyloxy)benzaldehyde (17): yellow solid; mp 58–61 °C (ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$, 360 MHz) 10.26 (s, 1 H, CHO), 8.30 (d, J = 2.16 Hz, 1 H, Ar H), 8.06 (d, J = 2.16 Hz, 1 H, Ar H), 4.24–4.21 (m, 2 H, $ArOCH_2$), 3.89–3.86 (m, 2 H, CH_2O), 3.75–3.72 (m, 2 H, OCH_2), 3.63–3.60 (m, 2 H, CH_2O), 2.07 (br s, 1 H, OH); ^{1}H NMR (DMSO-d_6, 360 MHz) 10.13 (s, 1 H, CHO), 8.41 (d, J = 2.17 Hz, 1 H, Ar H), 7.92 (d, J = 2.17 Hz, 1 H, Ar H), 4.18–4.15 (m, 2 H, $ArOCH_2$), 3.77–3.74 (m, 2 H, CH_2O), 3.7–3.4 (m, OCH_2CH_2OH and H_2O); ^{13}C NMR ($CDCl_3$, 90.56 MHz) 188.78, 161.36, 152.49, 137.77, 131.62, 94.15, 89.31, 75.53, 72.66, 69.97, 61.81; ^{13}C NMR (DMSO-d_6, 90.56 MHz) 188.90, 160.82, 151.59, 136.51, 131.27, 96.09, 90.24, 75.06, 72.10, 69.16, 59.87; MS m/z 462 (M^+).

Anal. Calcd for $C_{11}H_{12}I_2O_4$ (462): C, 28.59; H, 2.62. Found: C, 28.99; H, 3.03.

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Supplementary Material Available: IR and low resolution mass spectra of **2–17** (4 pages). Ordering information is given on any current masthead page.