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ECO-FRIENDLY SYNTHESIS OF NOVEL LARIAT ETHERS VIA MANNICH REACTION UNDER SOLVENTLESS CONDITIONS

Hashem Sharghi* and Reza Khalifeh

Department of Chemistry, Shiraz University, Shiraz, 71454, I. R. Iran
Fax:+98 711 2280926; E-mail: shashem@chem.susc.ac.ir.

Abstract – An expeditious solventless synthesis of novel lariat ethers using calcium oxide (CaO) via Mannich reaction are herein described. This methodology eliminates the use of excess of solvent during the course of reaction. The reaction time is brought down from hours to minutes (20-30 minutes) along with yield enhancement. The CaO powder can be reused up to three times after simple washing with acetone.

INTRODUCTION

More than thirty years have passed since Pederson's monumental discovery of the crown ethers.[1] Many synthetic approaches have been developed to prepare a multitude of macrocyclic ethers containing various heteroatoms and functional groups.[2] When one or more of the oxygen atoms in crown ethers are replaced with nitrogen atoms, aza-crown macrocycles result.[2, 3] The most convenient way to functionalize the azacrown ethers with proton ionizable side arms is to attach those side arms to the ring NH groups. Secondary nitrogens are able to undergo nucleophilic substitution with alkylating agents bearing protected or unprotected proton ionizable units.[4] Another possibility is the Mannich reactions that react readily with electron rich aromatics such as phenols.[5] The Mannich reaction, as a method for modification of azacrown ethers with hydroxybenzyl functions has some advantages when compared to alkylation of the azacrowns by benzyl halides. In fact, aminomethylation of the phenols allow the preparation of azamacrocycles containing both electron donationg and electron withdrawing groups in substituent phenolic rings. The preparation of such compounds by alkylation is not always convenient because of difficulties in preparing the starting benzyl halides and the necessity of protecting the phenolic hydroxyl group.[6] It is not easy to find a new general method to synthesize macrocyclic ligands, if the method is applicable for the formation of new molecular topologies. Obviously, the elaboration of general and simple approaches for the synthesis and functionalization of azacrown macrocycles remains a very important problem for researchers working in this field. One of the most important objectives now is to

adapt classical processes so that pollution effects are kept to a minimum, with both a reduction in energy and consumption of raw materials. In this respect, dry-media reactions are promising, and a new approach has been undertaken using CaO chemistry. Previously we have studied the use of CaO for preparation of oximes by reaction of various types of ketones and aldehydes with hydroxylamine hydrochloride under mild conditions.[7] As a part of our continued efforts to utilize the surface-mediated reaction(s) for developing Mannich reaction, here we wish to disclose a very simple, fast, general, highly efficient and improved one-step synthesis method for lariat ether containing phenolic group without any solvent in the presence of CaO in relatively high yields.

RESULTS AND DISCUSSION

The Mannich reaction is one of the most important multicomponent reactions in organic chemistry.[8] The Mannich reaction is a convenient method for the synthesis of azacrown ethers functionalized with phenolic sidearms.[9] We have previously shown that azacrown ether **2** was prepared by a simple and convenient procedure.[10] The initial work was concentrated on preparation of new lariat ethers.

To exploit a method for preparation of new lariat ethers **3-14**, the reaction of the azacrown ether **2** with *p-t*-butylphenol and paraformaldehyde via Mannich reaction was chosen as a model and its behavior was studied under a variety of conditions via TLC and NMR spectroscopy (Table 1).

Table 1. Mannich reaction of azacrown ether **2** with *p-t*-butylphenol under various conditions

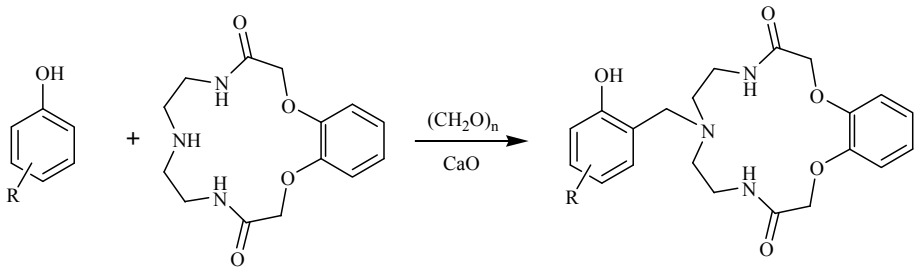
Entry	Conditions	T (ºC)	t (min)	Yield (%)[a]	Ref.
1	CCl_4	reflux	120	7	5
2	CCl_4/CaO	reflux	120	14	
3	benzene	reflux	120	10	11
4	benzene/CaO	reflux	120	20	
5	toluene	reflux	120	15	11
6	toluene / CaO	reflux	120	25	
7	Al_2O_3/MW		1.5	N.R.	12
8	(GMA)[b]	100	120	N.R.	13
9	(AMA)[c]	100	120	N.R.	14
10	CaO	70	3600	71	
11	CaO	100	20	75	
12	CaO	130	6	73	

[a] Isolated yields

[b] Graphite/CH_3SO_3H

[c] Al_2O_3/CH_3SO_3H

Condensation of paraformaldehyde with the azacrown ether **2** in the presence of *p*-*t*-butylphenol with appropriate solvent was carried out under reflux conditions (entries 1, 3, 5).[5,11] The final product **3** was obtained in 2 hours of heating with low yields (7-15%). We next screened CaO for Mannich reaction of aza-crown ether **2** under similar conditions. We found the yields were further improved to 14-25% (entries 2, 4, 6). In another study the effect of microwave was investigated and it was found that compound **3** was not prepared by this condition (entry 7).[12] In an attempt to "greenfiy" the synthetic procedure and increase its rate and yield experiments were done under solven-free condition. During the course of our studies aimed at developing solvent-free procedures,[7,13,14,15] we have now discovered that CaO alone promotes a very efficient Mannich reaction of activated and unactivated phenol compounds with azacrown ether **2** and paraformaldehyde at 100°C in high yield, without any of the environmental disadvantages of using toxic solvents (Scheme 1).



Scheme 1.

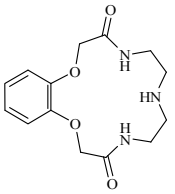
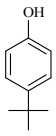
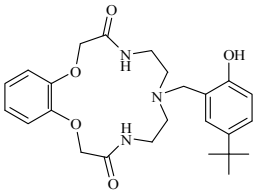
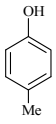
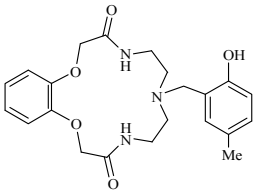
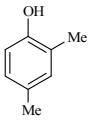
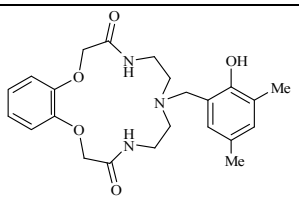
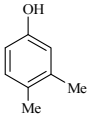
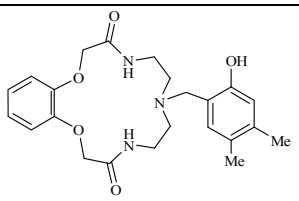
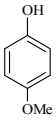
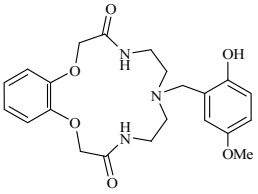
To the best of our knowledge there is no previous report of the Mannich reaction for preparation of lariat ethers by CaO. In a typical experiment, CaO, azacrown ether **2**, *p*-*t*-butylphenol and paraformaldehyde were mixed thoroughly. The mixture was heated in an oil bath at 100°C with stirring for 20 minutes until the reaction was completed. The product was isolated by simple extraction of the solid mass by acetone followed by the usual workup. To establish the generality and applicability of this method, various phenols with both electron-donating and -withdrawing substituents were subjected to the same reaction conditions as **3** to furnish the corresponding new lariat ethers **4-14**. Formation of benzylamine bonds occurred when the phenols had either electron-donating or electron-withdrawing substituents very rapidly within 20-30 minutes. The results of the Mannich reaction of azacrown ether **2** are collected in Table 2 (entries 1-12).

When *para*-substituted or unsubstituted phenols were used for the Mannich reaction with azacrown ether **2** in the presence of paraformaldehyde, macrocyclic ligands **4-14** were obtained in relatively high yields, although the yields drop as strongly electron-withdrawing substituents are added, as in **14**. The moderate yield of **14** is attributed to the relatively weak nucleophilicity of *para*-nitrophenol and its anion.[11] Aminomethylation of phenols with Mannich reaction usually occurs in the position *ortho* to the phenolic OH group even if the *para* position is unsubstituted (entry 6).[5] Possibly preferential attack on the *ortho* positions is caused by formation of a six membered transition state where the phenolic proton activates

the aminomethylating reagent.[17] This makes possible the introduction of chromogenic functions onto the phenol ring. The Mannich reaction of azacrown ether **2** with *p*-*t*-butylphenol on a 30 mmol scale proceeded just as well as the 1 mmol reaction.

Other aliphatic amines were efficiently converted to the desired products in excellent yields (Table 3, entries 1-6). For example the reaction between piperazine and two moles of *p*-*t*-butylphenol under conventional heating (reflux in benzene) was completed in 18-22 h in 40% yields, whereas the same reaction gave **20** in excellent yield (entry 6 in Table 3) under solventless condition within 24 minutes.

Table 2. Mannich reaction of azacrown ether **2** with phenols

Entry	Substrate	Phenols	Product	Yield (%)	Time (min)
1	 **2**		 **3**	75	20
2	**2**		 **4**	85	22
3	**2**		 **5**	88	25
4	**2**		 **6**	90	27
5	**2**		 **7**	75	23

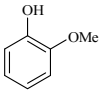
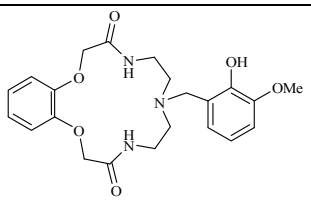
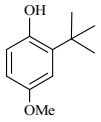
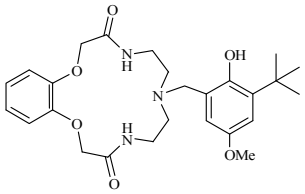
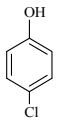
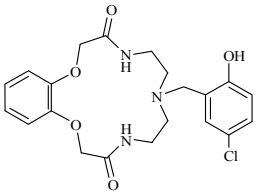
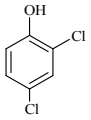
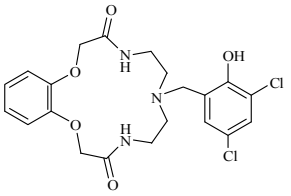
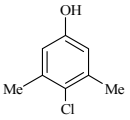
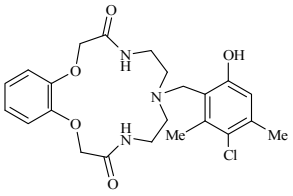
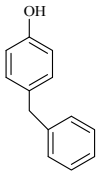
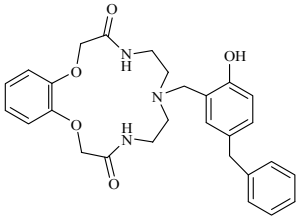
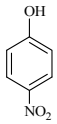
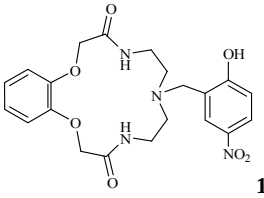
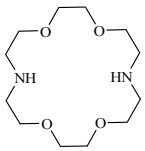
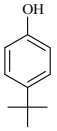
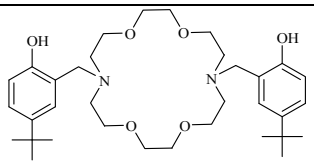
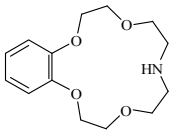
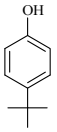
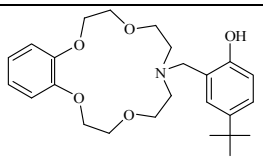
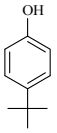
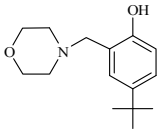
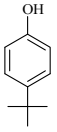
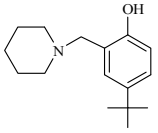
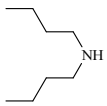
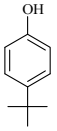
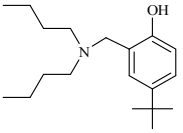
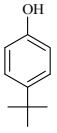
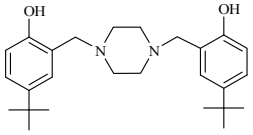
6	**2**		 **8**	74	23
7	**2**		 **9**	73	20
8	**2**		 **10**	76	26
9	**2**		 **11**	72	28
10	**2**		 **12**	79	27
11	**2**		 **13**	79	25
12	**2**		 **14**	40	30

Table 3. Mannich reaction of other azacrown ethers and amines with *p*-*t*-butylphenol

Entry	Substrate	Phenols	Product	Yield (%)	Time (min)
1			 **15**	75	27
2			 **16**	74	25
3			 **17**	88	20
4			 **18**	89	20
5			 **19**	79	20
6			 **20**	87	24

No attempt has been made to probe the mechanism of the reaction. Furthermore, catalytic activity of the recovered catalyst (CaO) was examined. The yields of macrocyclic **3** in second and third uses of the catalyst were almost same as that in the first use. In every case >90% of the CaO was easily recovered from reaction mixture by simple washing with acetone.

In conclusion, we have described a novel and highly efficient solvent-free protocol for Mannich reaction of phenol compounds using nontoxic and inexpensive CaO powder. The advantages of this environmentally benign and safe protocol include a simple reaction setup not requiring specialized

equipment, mild reaction conditions, high product yields, very short reaction times, and the elimination of solvents.

Complexation studies behaviors for these new lariat aza-crown ethers are in progress and will be reported in more detail at a later date.

EXPERIMENTAL

Instrumentation, Analysis and Starting Material

NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) spectrometer in pure deuterated solvents with tetramethylsilane as an internal standard. Infrared spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instruments at 70 or 20 ev. Melting points determined in open capillary tubes in a Büchi-535 circulating oil melting point apparatus. UV/Vis. Spectra was obtained with an Ultrospec 3000 UV/Visible spectrometer. Elemental analyses were performed at the National Oil Co. of Iran, Tehran Research Center. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel PolyGram SILG/UV 254 plates. Column chromatography was carried out on short columns of silica gel 60 (70-230 mesh) in glass columns (2-3 cm diameter) using 15-30 gram of silica gel per one gram of crude mixture. Chemical materials were either prepared in our laboratories or were purchased from Fluka, Aldrich and Merck Companies.

General procedure for compounds 3-14

Azacrown ether **2** (1 mmol), phenol (1.2 mmol), paraformaldehyde (1.2 mmol) and CaO (1 g) were thoroughly mixed. The resulting fine powder was transferred to a round-bottom flask and stirred in an oil bath at 100 º C for the 20-30 min. After cooling, acetone was added to the mixture and CaO was removed by filtration. Evaporation of the solvent under reduced pressure gave the crude products, which were purified by flash column chromathography (eluent: *n*-hexane/ EtOAc 1/1) or recrystallized from EtOAc.

General procedure for compounds 15-20

Secondary amines (1 mmol), *p*-*t*-butylphenol (1.2 mmol), paraformaldehyde (1.2 mmol) and CaO (1 g) were thoroughly mixed. The resulting fine powder was transferred to a round-bottom flask and stirred in an oil bath at 100 º C for the 20-30 min. After cooling, acetone was added to the mixture and CaO was removed by filtration. Evaporation of the solvent under reduced pressure gave the crude products, which were purified by flash column chromathography.

7-(5-*tert*-Butyl-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclo-pentadecine-3,11(4*H*,12*H*)dione (3)

Compound **3** was obtained as white powder in 75% yield. Mp 216 °C. IR (KBr): 3377(s), 3281(br),

2955(m), 2906(m), 1676(vs), 1597(m), 1539(s), 1506(s), 1439(m), 1346(s), 1263(s), 1225(m), 1128(s), 1051(s), 820(m), 725(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.23(s, 9H), 2.74(t, 4H, *J*=5.3 Hz), 3.52(t, 4H, *J*=5.3 Hz), 3.73(s, 2H), 4.44(s, 4H), 6.68(d, 1H, *J*=8.4 Hz), 6.84-7.01(m, 4H), 7.04(s, 1H), 7.11(d, 1H, *J*=8.4 Hz), 7.62(s, 2H), 8.44(s, 1H). ^{13}C NMR ($CDCl_3$): δ 31.5, 33.9, 35.7, 52.8, 54.4, 68.0, 114.1, 115.2, 121.4, 122.6, 125.8, 127.1, 142.5, 147.0, 153.6, 167.9. MS m/z (%): 456(M^++1, 0.6), 455(M^+, 2.8), 384(1.7), 383(6.7), 294(1.7), 293(3.9), 292(28.7), 225(30.9), 204(21.9), 163(48.9), 147(36.5), 119(37.1), 85(72.5), 69(71.3), 56(100). Anal. Calcd for $C_{25}H_{33}N_3O_5$ (455.547): C, 65.91; H, 7.30; N, 9.22. Found: C, 66.07; H, 7.41; N, 9.05. UV($CHCl_3$): λ_{max}(log ε) 245(2.96), 267(3.23), 282(3.19) nm.

7-(2-Hydroxy-5-methylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (4)

Compound **4** was obtained as white powder in 85% yield. Mp 206 °C. IR (KBr): 3400(s), 3200(br), 2900(m), 2860(m), 2680(vs), 1662(vs), 1598(m), 1540(s), 1506(s), 1438(m), 1259(s), 1215(s), 1128(s), 1047(s), 815(s), 740(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.22(s, 3H), 2.75(t, 4H, *J*=5.3 Hz), 3.54(t, 4H, *J*=5.3 Hz), 3.73(s, 2H), 4.51(s, 4H), 6.64(d, 1H, *J*=8.0 Hz), 6.87-7.07(m, 6H), 7.56(s, 2H), 8.14(s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.8, 36.2, 53.3, 56.0, 68.7, 114.9, 116.1, 122.4, 123.2, 129.5, 130.0, 131.0, 147.6, 154.0, 168.3. MS m/z (%): 415(M^++2, 1.2), 414(M^++1, 4.2), 413(M^+, 10.0), 396(2.4), 341(16.5), 292(37.7), 225(41.9), 206(15.5), 180(12.3), 176(23.2), 162(27.5), 121(93.3), 91(85.4), 85(60.8), 69(60.0), 56(86.6), 43(100.0). Anal. Calcd for $C_{22}H_{27}N_3O_5$ (413.467): C, 63.91; H, 6.58; N, 10.16. Found: C, 63.75; H, 6.43; N, 9.87. UV($CHCl_3$): λ_{max}(log ε) 244(3.04), 271(3.33) nm.

7-(2-Hydroxy-3,5-dimethylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (5)

Compound **5** was obtained as white powder in 88% yield. Mp 157 °C. IR (KBr): 3323(br), 2914(m), 2818(m), 1662(vs), 1541(s), 1502(s), 1439(m), 1259(s), 1161(m), 1122(s), 1047(s), 746(s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.96(s, 3H), 2.17(s, 3H), 2.72(t, 4H, *J*=5.3 Hz), 3.50(t, 4H, *J*=5.3 Hz), 3.70(s, 2H), 4.49(s, 4H), 6.65(s, 1H), 6.79(s, 1H), 6.91-7.05(m, 4H), 7.49(s, 2H), 8.41(s, 1H). ^{13}C NMR ($CDCl_3$): δ 15.2, 20.3, 35.7, 52.7, 57.1, 68.5, 114.9, 121.2, 122.9, 124.2, 127.6, 128.5, 131.0, 147.3, 151.8, 168.0. MS m/z (%):429(M^++2, 4.5), 428(M^++1, 21), 427(M^+, 40.6), 410(3.4), 356(4.9), 355(20.9), 294(10.1), 293(8.6), 292(30.0), 225(37.2), 176(27.8), 150(20.2), 135(83.2), 91(93.6), 85(78.1), 69(78.9), 56(100). Anal. Calcd for $C_{23}H_{29}N_3O_5$ (427.494): C, 64.62; H, 6.84; N, 9.83. Found: C, 64.44; H, 6.69; N, 10.04. UV($CHCl_3$): λ_{max}(log ε) 246(3.05), 269(3.23), 287(3.20) nm.

7-(2-Hydroxy-4,5-dimethylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (6)

Compound **6** was obtained as white powder in 90% yield. Mp 214 °C. IR (KBr): 3389(s), 3279(br), 2967(m), 2824(m), 1674(vs), 1545(m), 1504(s), 1456(m), 1261(s), 1124(s), 1047(s), 746(s) cm^{-1}. ^1H

NMR ($CDCl_3$): δ 2.10(s, 3H), 2.12(s, 3H), 2.72(t, 4H, *J*=5.3 Hz), 3.50(t, 4H, *J*=5.3 Hz), 3.67(s, 2H), 4.46(s, 4H), 6.53(s, 1H), 6.79(s, 1H), 6.89-7.00(m, 4H), 7.60(s, 2H), 8.03(s, 1H). ^{13}C NMR ($CDCl_3$): δ 18.6, 19.5, 35.8, 52.7, 54.2, 68.1, 114.2, 117.1, 119.3, 122.6, 127.6, 131.3, 137.3, 147.1, 153.6, 167.9. MS m/z (%): 428(M^++1, 1.2), 427(M^+, 3.8), 355(10.6), 294(2.8), 293(5.2), 292(18.9), 251(3.8), 225(37.4), 206(8.7), 190(8.7), 180(14.2), 176(18.3), 135(76.0), 91(100), 69(72.2), 56(97.7). Anal. Calcd for $C_{23}H_{29}N_3O_5$ (427.494): C, 64.62; H, 6.84; N, 9.83. Found: C, 64.48; H, 6.65; N, 10.02. UV($CHCl_3$): λ_{max}(log ε) 246(3.04), 268(3.23), 287(3.21) nm.

7-(2-Hydroxy-5-methoxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (7)

Compound **7** was obtained as white powder in 75% yield. Mp 205.5 °C. IR (KBr): 3410(s), 3254(br), 2955(m), 2818(m), 1684(vs), 1547(s), 1508(s), 1497(s), 1437(m), 1254(s), 1219(s), 1125(s), 1049(s), 754(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.74(t, 4H, *J*=5.3 Hz), 3.51(t, 4H, *J*=5.3 Hz), 3.70(s, 3H), 3.72(s, 2H), 4.49(s, 4H), 6.62-6.67(m, 3H), 6.89-7.06(m, 4H), 7.51(s, 2H), 7.97(s, 1H). ^{13}C NMR ($CDCl_3$): δ 35.8, 53.0, 55.6, 56.1, 68.4, 113.8, 114.6, 115.8, 116.4, 122.8, 123.0, 147.2, 149.7, 153.0, 167.9. MS m/z (%): 431(M^++2, 0.6), 430(M^++1, 4.7), 429(M^+, 11.6), 357(3.2), 294(6.1), 293(4.7), 292(12.5), 225(43.0), 167(19.2), 136(39.2), 85(59.9), 69(87.2), 56(100). Anal. Calcd for $C_{22}H_{27}N_3O_6$ (429.466): C, 61.53; H, 6.34; N, 9.78. Found: C, 61.69; H, 6.50; N, 9.61. UV($CHCl_3$): λ_{max}(log ε) 247(3.22), 267(3.24), 302(3.35) nm.

7-(2-Hydroxy-3-methoxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (8)

Compound **8** was obtained as white powder in 74% yield. Mp 199 °C. IR (KBr): 3529(s), 3410(s), 2910(m), 2843(m), 2180(m), 1686(vs), 1595(m), 1531(s), 1506(s), 1479(s), 1433(m), 1346(s), 1263(s), 1219(m), 1124(s), 1072(s), 1047(s), 818(m), 752(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.71(t, 4H, *J*=5.3 Hz), 3.48(t, 4H, *J*=5.3 Hz), 3.68(s, 2H), 3.74(s, 3H), 4.42(s, 4H), 6.20(s, 1H), 6.71-6.79(m, 3H), 6.88-7.04(m, 4H), 7.86(s, 2H). ^{13}C NMR ($CDCl_3$): δ 35.6, 51.3, 52.4, 55.9, 67.8, 110.3, 113.0, 113.5, 119.3, 122.3, 123.3, 144.3, 146.7, 167.3. MS m/z (%):431(M^++2, 15.0), 430(M^++1, 60.7), 429(M^+, 35.9), 412(10), 357(21.9), 294(22), 293(11.6), 292(45.8), 225(26.6), 192(29.7), 137(100), 121(25.3), 85(75.3), 69(55.8), 56(97.5). Anal. Calcd for $C_{22}H_{27}N_3O_6$ (429.466): C, 61.53; H, 6.34; N, 9.78. Found: C, 61.66; H, 6.17; N, 9.59. UV($CHCl_3$): λ_{max}(log ε) 247(3.16), 264(3.28), 283(3.21) nm.

7-(3-*tert*-Butyl-2-hydroxy-5-methoxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (9)

Compound **9** was obtained as white powder in 73% yield. Mp 186 °C. IR (KBr): 3306(br), 2949(m), 2829(m), 1688(vs), 1545(s), 1504(s), 1437(s), 1261(s), 1236(s), 1159(s), 1047(s), 746(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.10(s, 9H), 2.78(t, 4H, *J*=5.3 Hz), 3.56(t, 4H, *J*=5.3 Hz), 3.72(s, 3H), 3.74(s, 2H), 4.48(s, 4H),

6.42(d, 1H, *J*=2.97 Hz), 6.72(d, 1H, *J*=2.97 Hz), 6.88-7.04(m, 4H), 7.32(s, 2H), 9.38(s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.9, 34.5, 35.5, 52.8, 55.6, 58.6, 68.2, 111.4, 113.0, 114.6, 122.0, 122.8, 137.9, 147.1, 149.3, 152.2, 168.1. MS m/z (%): 487(M^++2, 4.6), 486(M^++1, 17.0), 485(M^+, 34.6), 414(1.4), 413(4.2), 384(1.1), 313(0.6), 294(5.4), 293(5.6), 292(13.9), 225(62.8), 192(71.6), 177(43.3), 149(48.7), 121(26.4), 85(47.8), 69(100), 56(80.4). Anal. Calcd for $C_{26}H_{35}N_3O_6$ (485.573): C, 64.31; H, 7.27; N, 8.65. Found: C, 64.16; H, 7.14; N, 8.80. UV($CHCl_3$): λ_{max}(log ε) 247(3.20), 270(3.22), 300(3.43) nm.

7-(5-Chloro-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (10)

Compound **10** was obtained as white powder in 76% yield. Mp 237 °C (decomp.). IR (KBr): 3394(s) 3250(br), 2950(m), 2850(m), 1662(vs), 1590(m), 1540(s), 1500(s), 1427(s), 1370(m), 1245(s), 1210(m), 1128(s), 1056(s), 823(s), 756(s), 653(s) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.64(t, 4H, *J*=5.3 Hz), 3.40(t, 4H, *J*=5.3 Hz), 3.54(s, 2H), 4.44(s, 4H,), 6.72(d, 1H, *J*=8.6 Hz), 6.95-7.27(m, 5H), 7.27(d, 1H, *J*=2.2 Hz), 7.80(s, 2H), 9.78(s, 1H). ^{13}C NMR (DMSO-d_6): δ 35.4, 50.1, 52.2, 68.0, 114.4, 116.8, 122.2, 122.7, 127.0, 127.6, 129.5, 147.2, 154.8, 167.2. MS m/z (%): 435(M^++2, 0.4), 434(M^++1, 0.2), 433(M^+, 2.2), 416(0.3), 361(2.3), 292(12.7), 225(24.3), 196(11.1), 167(12.6), 141(16.9), 121(19.4), 113(19.9), 85(50.9), 77(60.3), 69(66.2), 56(97.9), 43(100.0). Anal. Calcd for $C_{21}H_{24}ClN_3O_5$ (433.885): C, 58.13; H, 5.58; N, 9.68. Found: C, 57.89; H, 5.76; N, 9.90. UV($CHCl_3$): λ_{max}(log ε) 246(3.13), 272(3.24), 292(3.25), 360(2.97) nm.

7-(3,5-Dichloro-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (11)

Compound **11** was obtained as white powder in 72% yield. Mp 205 °C. IR (KBr): 3306(br), 3067(m), 2900(m), 2829(m), 1662(vs), 1541(m), 1502(s), 1456(s), 1261(s), 1122(s), 1047(s), 752(s) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.57(t, 4H, *J*=5.3 Hz), 3.31(t, 4H, *J*=5.3 Hz), 3.57(s, 2H), 4.36(s, 4H), 6.84-7.18(m, 6H), 7.97(s, 2H), 10.36(s, 1H). ^{13}C NMR (DMSO-d_6): δ 34.7, 50.8, 52.5, 68.6, 115.3, 120.8, 122.3, 122.5, 127.1, 127.4, 127.7, 147.4, 150.8, 167.4. MS m/z (%): 469(M^++1, 0.2), 468(M^+, 0.2), 467(0.9), 294(2.1), 293(4.1), 292(15.2), 230(9.4), 225(23.7), 206(11.3), 175(17.9), 167(15.0), 150(12.8), 121(23.1), 111(29.7), 85(53.6), 69(63.9), 56(100). Anal. Calcd for $C_{21}H_{23}Cl_2N_3O_5$ (468.330): C, 53.86; H, 4.95; N, 8.97. Found: C, 53.98; H, 4.81; N, 9.16. UV($CHCl_3$): λ_{max}(log ε) 246(3.13), 269(3.23), 293(3.25) nm.

7-(3-Chloro-6-hydroxy-2,4-dimethylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (12)

Compound **12** was obtained as white powder in 79% yield. Mp 241 °C (decomp.). IR (KBr): 3375(s), 3190(br), 2878(s), 2806(m), 1657(vs), 1599(s), 1541(s), 1506(s), 1438(s), 1211(s), 1122(s), 1063(s), 815(m), 744(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.26(s, 3H), 2.33(s, 3H), 2.75(t, 4H, *J*=5.3 Hz), 3.54(t, 4H, *J*=5.3 Hz), 3.83(s, 2H), 4.51(s, 4H), 6.50(s, 1H), 6.91-7.07(m, 4H), 7.41(s, 2H), 9.43(s, 1H). ^{13}C NMR

($CDCl_3$): δ= 16.9, 21.1, 35.8, 52.8, 53.8, 68.6, 115.1, 116.1, 118.9, 123.0, 136.8, 139.0, 147.3, 154.8, 168.1. MS m/z (%): 463(M^++2, 0.3), 462(M^++1,1.2), 461(M^+, 3.6), 390(0.3), 389(2.4), 294(5.0), 293(5.6), 292(15.4), 225(50.0), 180(14.3), 168(32.8), 150(18.0), 121(31.1), 105(81.7), 85(64.5), 69(89.3), 56(100). Anal. Calcd for $C_{23}H_{28}ClN_3O_5$ (461.938): C, 59.80; H, 6.11; N, 9.10. Found: C, 59.95; H, 6.01; N, 9.27. UV($CHCl_3$): λ_{max}(log ε) 246(3.15), 271(3.21) nm.

7-(5-Benzyl-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (13)

Compound **13** was obtained as white powder in 79% yield. Mp 227 °C (decomp.). IR (KBr): 3396(s), 3234(br), 2914(m), 2849(m), 1676(vs), 1599(m), 1541(s), 1508(s), 1437(s), 1261(s), 1221(s), 1130(s), 1059(s), 820(m), 752(s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.72(t, 4H, *J*=5.3 Hz), 3.51(t, 4H, *J*=5.3 Hz), 3.71(s, 2H), 3.84(s, 2H), 4.49(s, 4H), 6.64(d, 1H, *J*=8.0 Hz), 6.84-7.30(m, 11H), 7.49(s, 2H), 8.30(s, 1H). ^{13}C NMR ($CDCl_3$): δ 35.8, 40.9, 52.9, 56.1, 68.4, 114.6, 115.9, 122.8, 126.0, 128.4, 128.8., 129.6, 130.3, 132.6, 147.2, 154.3, 168.0. MS m/z (%): 490(M^++1, 0.2), 489(M^+, 1.2), 418(0.3), 417(4.3), 294(2.9), 293(5.8), 292(16.6), 225(46.9), 196(28.3), 167(51.9), 153(21.9), 121(25.9), 85(55.1), 69(70.9), 56(100). Anal. Calcd for $C_{28}H_{31}N_3O_5$ (489.563): C, 68.69; H, 6.38; N, 8.58. Found: C, 68.52; H, 6.45; N, 8.77. UV($CHCl_3$): λ_{max}(log ε) 248(3.22), 265(3.26), 287(3.21) nm.

7-(2-Hydroxy-5-nitrobenzyl)-5,6,7,8,9,10-hexahydro-2*H*-benzo[*b*][1,4,7,10,13]dioxatriazacyclopentadecine-3,11(4*H*,12*H*)dione (14)

Compound **14** was obtained as yellow powder in 40% yield. Mp 239.5 °C (decomp.). IR (KBr): 3390(s), 3200(br), 2850(m), 1667(vs), 1600(s), 1550(vs), 1530(vs), 1500(s), 1440(s), 1335(vs), 1295(s), 1257(s), 1218(s), 1128(s), 1085(m), 1056(s), 830(m), 817(m), 750(s) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.51(t, 4H, *J*=5.3 Hz), 3.37(t, 4H, *J*=5.3 Hz), 3.65(s, 2H), 4.40(s, 4H), 6.89(d, 1H, *J*=8.9 Hz), 6.96-7.11(m, 4H), 7.80(s, 2H), 7.95(dd, 1H, *J*=8.9, 2.3 Hz), 8.11(d, 1H, *J*=2.2 Hz). ^{13}C NMR (DMSO-d_6): δ 35.5, 50.6, 52.4, 68.3, 114.7, 115.6, 122.4, 124.7, 126.0, 126.3, 126.6, 139.7, 147.4, 162.6, 167.4. MS m/z (%): 445(M^++1, 0.3), 444(M^+, 1.3), 427(14.3), 414(0.5), 356(0.4), 340(0.4), 292(4.9), 225(39.2), 207(10.6), 193(5.3), 180(9.7), 167(20.5), 150(19.3), 121(22.3), 113(18.0), 85(48.7), 69(80.7), 56(92.4), 43(100.0). Anal. Calcd for $C_{21}H_{24}N_4O_7$ (444.438): C, 56.75; H, 5.44; N, 12.61. Found: C, 56.68; H, 5.39; N, 12.43. UV(DMSO): λ_{max}(log ε) 298(3.45), 354(3.43) nm.

2,2′-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecan-7,16-diyl)bis(methylene)bis(4-*tert*-butylphenol) (15)

Compound **15** was obtained as white powder in 75% yield. Mp 165-166 °C, (Lit.,[11a] 173-174 ºC); ^{1}H NMR ($CDCl_3$): δ 1.19(s, 18H), 2.78(t, 8H, *J*=5.4 Hz), 3.53(s, 8H), 3.59(t, 8H, *J*=5.4 Hz), 3.72(s, 4H), 6.67(d, 1H, *J*=8.4 Hz), 6.88(d, 1H, *J*=2.2 Hz), 7.10(dd, 1H, *J*=8.4, 2.4 Hz), 10.31(s, 2H). ^{13}C NMR ($CDCl_3$): δ 31.6, 33.9, 53.6, 59.1, 69.2, 70.8, 115.6, 121.5, 125.3, 125.4, 141.6, 155.5

4-*tert*-Butyl-2-((5,6,8,9,11,12-hexahydro-2*H*-benzo[*e*][1,4,7,10,13]tetraoxazacyclopentadecin-7(3*H*)-yl)methyl)phenol (16) [17]

Compound **16** was obtained in 74% yield. ^{1}H NMR ($CDCl_3$): δ 1.18(s, 9H), 2.79(t, 4H, *J*=5.8 Hz), 3.68-3.84(m, 10H), 4.06(t, 4H, *J*=4.0 Hz), 6.63(d, 1H, *J*=8.4 Hz), 6.78-6.82(m, 4H), 6.86(d, 1H, *J*=2.0 Hz), 7.07(dd, 1H, *J*=8.4, 2.3 Hz), 9.79(s, 1H). ^{13}C NMR ($CDCl_3$): δ 31.6, 33.9, 54.1, 60.1, 69.4, 69.6, 114.3, 115.7, 121.5, 125.4, 125.5, 141.6, 149.1, 155.5 Anal. Calcd for $C_{25}H_{35}NO_5$ (429.549): C, 69.90; H, 8.21; N, 3.26. Found: C, 69.72; H, 8.43; N, 3.44.

4-*tert*-Butyl-2-(morpholinomethyl)phenol (17)

Compound **17** was obtained in 88% yield. Mp 76-78 °C, (Lit.,[18] 75-78 ºC). ^{1}H NMR ($CDCl_3$): δ 1.21(s, 9H), 2.50(s, 4H), 3.62(s, 2H), 3.67(t, 4H, *J*=4.5 Hz), 6.68(dd, 1H, *J*=8.5, 2.8 Hz), 6.90(d, 1H, *J*=2.2 Hz), 7.12(dd, 1H, *J*=8.5, 2.2 Hz), 9.74(s, 1H). ^{13}C NMR ($CDCl_3$): δ 31.6, 33.9, 52.9, 62.5, 66.7, 114.9, 115.5, 119.9, 125.6, 141.9, 154.9. Anal. Calcd for $C_{15}H_{23}NO_2$ (249.349): C, 72.25; H, 9.30; N, 5.62. Found: C, 72.03; H, 9.47; N, 5.41.

4-*tert*-Butyl-2-(piperidin-1-ylmethyl)phenol (18)

Compound **18** was obtained in 89% yield. Mp 46-47 °C, (Lit.,[18] 47-48 ºC). ^{1}H NMR ($CDCl_3$): δ 1.18(s, 9H), 1.38-1.55(m, 6H), 2.18-2.42(m, 4H), 3.56(s, 2H), 6.66(dd, 1H, *J*=8.5, 2.6 Hz), 6.86(d, 1H, *J*=2.3 Hz), 7.08(dd, 1H, *J*=8.5, 2.4 Hz), 10.77(s, 1H).^{13}C NMR ($CDCl_3$): δ 24.1, 26.2, 31.7, 33.7, 53.9, 62.6, 115.9, 121.4, 125.7, 126.1, 141.4, 155.7. Anal. Calcd for $C_{16}H_{25}NO$ (247.376): C, 77.68; H, 10.19; N, 5.66. Found: C, 77.45; H, 10.31; N, 5.85.

4-*tert*-Butyl-2-[(dibutylamino)methyl]phenol (19)

Compound **19** was obtained as yellow oil in 79% yield. (Lit.[19]) ^{1}H NMR ($CDCl_3$): δ 0.81(t, 6H, *J*=7.2 Hz), 1.19(s, 9H), 1.23-1.50(m, 8H), 2.42(t, 4H, *J*=7.2 Hz), 3.65(s, 2H), 6.64(d, 1H, *J*=8.4 Hz), 6.86(s, 1H), 7.07(dd, 1H, *J*=8.4, 2.3 Hz), 11.02(s, 1H). ^{13}C NMR ($CDCl_3$): δ 15.1, 21.5, 29.8, 32.3, 34.5, 54.1, 59.4, 116.9, 122.3, 125.6, 126.0, 142.1, 156.7. Anal. Calcd for $C_{19}H_{33}NO$ (291.471): C, 78.29; H, 11.41; N, 4.81. Found: C, 78.07; H, 11.63; N, 4.97.

2,2′-(Piperazine-1,4-diylbis(methylene))bis (4-*tert*-buty)phenol (20) [20]

Compound **20** was obtained as white powder in 87% yield. Mp 258 °C. ^{1}H NMR ($CDCl_3$): δ= 1.20(s, 18H), 2.03-3.10(m, 8H), 3.65(s, 4H), 6.68(d, 1H, *J*=8.5 Hz), 6.90(d, 1H, *J*=2.3 Hz), 7.12(dd, 1H, *J*=8.5, 2.4 Hz), 10.32(s, 2H). ^{13}C NMR ($CDCl_3$): δ 31.6, 33.9, 52.4, 61.6, 115.5, 120.0, 125.5, 142.1, 155.0. Anal. Calcd for $C_{26}H_{38}N_2O_2$ (410.529): C, 76.06; H, 9.33; N, 6.82. Found: C, 75.84; H, 9.19; N, 6.69.

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