Reaction on a solid surface — A simple, economical, and efficient Mannich reaction of azacrown ethers over graphite

Hashem Sharghi and Reza Khalifeh

Abstract: Graphite brings about a rapid Mannich reaction with a range of activated and unactivated phenolic compounds such as *p*-cresol and *p*-nitrophenol. The reactions are carried out with azacrown ether and paraformaldehyde in solvent-free conditions at 100 °C for 20–30 min. The graphite powder can be reused up to three times after simple washing with acetone.

Key words: azacrown ether, lariat ether, graphite, solvent-free, Mannich reaction.

Résumé : Le graphite en poudre permet de réaliser des réactions de Mannich rapides de composés phénoliques activés et non activés, tel le *p*-crésol et le *p*-nitrocrésol, avec un éther azacouronne et le paraformaldéhyde, dans des conditions sans solvant, à 100 °C, pendant 20 à 30 minutes. On peut réutiliser le graphite en poudre jusqu'à trois fois après un simple lavage avec de l'acétone.

Mots-clés : éther azacouronne, éther lariat, graphite, sans solvant, réaction de Mannich.

[Traduit par la Rédaction]

Introduction

Azacrown ethers are often used as precursors for structurally modified macrocyclic ion-complexing agents because of the attachment of pendant groups to the secondary nitrogen atom (1). The major methods for functionalizing azacrown macrocycles with proton-ionizable phenol groups include the treatment of an azacrown ether with a benzyl or benzoyl halide and reductive amination with aromatic aldehydes. These methods are not always convenient because of the difficulties in preparing the starting materials, the need to reduce the carbonyl group if carboxylic acid derivatives are used, and the need to protect the phenolic hydroxy group (2). The Mannich reaction, as a method for modification of azacrown macrocycles with hydroxybenzyl functions, has some advantages when compared to alkylation of the azacrowns by benzyl halides. In fact, aminomethylation of the phenols allows the preparation of azamacrocycles containing both electron-donating and electron-withdrawing groups in the substituent phenolic rings (3). In spite of appreciable interest in the azacrown macrocycles, they are still not readily available for study because they are either very expensive or difficult to prepare. 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 a reduction both in energy and in consumption of raw materials. In this respect, dry-media reactions are promising, and a new approach has been undertaken using graphite chemistry. The exceptional ability of graphite to adsorb organic molecules is well known (4). Diels–Alder and ene reactions (5), decarboxylations (5*a*, 5*b*), decompositions (6), rearrangements (5*a*, 5*b*, 7), keto carboxylation (8), conversion of aldehydes into nitriles (9), Friedel–Crafts acylation of aromatic compounds (10), alkylation of aromatic compounds and alcohols (11*a*), and dehydration of secondary alcohols (11*b*) were all effected using such conditions.

As a part of our continued efforts to utilize surface-mediated reactions for conducting Mannich reaction, here we wish to disclose a very simple, fast, general, highly efficient, and improved one-step method for synthesizing lariat ether containing phenolic groups. The reaction occurs without any solvent in the presence of graphite and gives relatively high yields.

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Results and discussion

The Mannich reaction is one of the most important tools for synthesizing new compounds (12). The most important applications of this reaction are in the pharmaceutical chemistry and natural product chemistry (12, 13). Also the Mannich reaction is known to be a powerful method for functionalizing azacrown ethers with additional ligating units (3, 14). The Mannich reaction consist of the condensation of a substrate (R–H) possessing at least one active hydrogen (alkyl ketones, phenols, NH heterocycles, etc) with formaldehyde (or occasionally other aldehydes) and a primary or secondary amine (or occasionally ammonia). Although numerous methods to achieve Mannich reaction are

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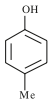
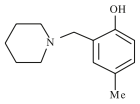
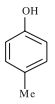
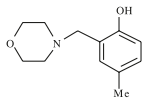
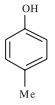
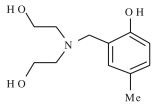
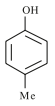
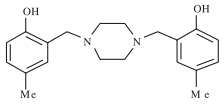
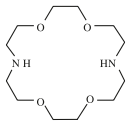
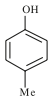
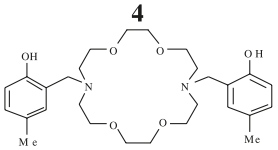
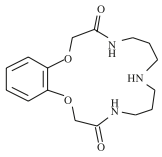
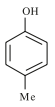
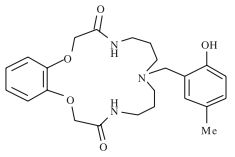
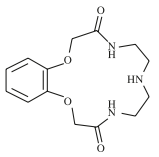
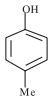
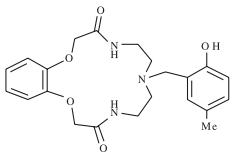
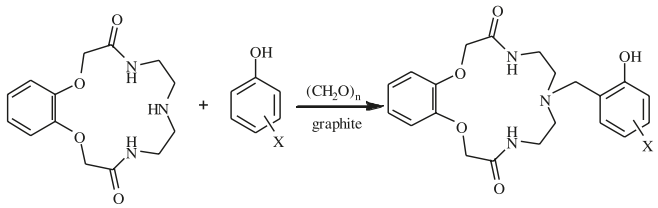
Table 1. Mannich reaction of other azacrown ethers and amines with *p*-cresol

Entry	Substrate	Phenols	Product	Yield (%)
1			 **1**	90
2			 **2**	96
3			 **3**	82
4			 **4**	85
5			 **5**	88
6	 **6**		 **7**	84
7	 **8**		 **9**	87

known, newer methods continue to attract attention for their experimental simplicity and effectiveness. We have been interested in the development of methods for Mannich reactions that (a) would avoid the use of added acids, (b) would avoid aqueous workup, (c) are easy to perform, and (d) are economical for application to large-scale preparations.

We have previously shown that azacrown ether **8** can be prepared by a simple and convenient procedure (15). Because graphite has a large surface area, it is a good heat conductor, and the reaction can be carried out under milder conditions (7). During the course of our studies aimed at developing solvent-free procedures (9, 10, 16, 19, 20), we have now discovered that graphite alone promotes a very efficient Mannich reaction of activated and unactivated phenol compounds with azacrown ether **8** and paraformaldehyde at 100 °C in high yields, without any of the environmental disadvantages of using toxic solvents (Scheme 1). In a typical experiment, graphite, azacrown ether **8**, *p*-cresol, and paraformaldehyde were mixed thoroughly. The mixture was heated in an oil bath at 100 °C with stirring for 20 min until

Scheme 1.

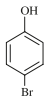
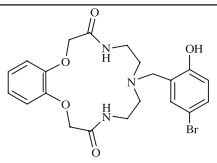
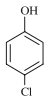
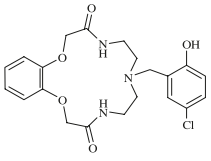
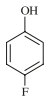
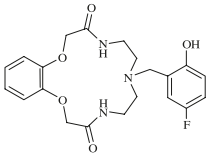
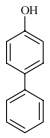
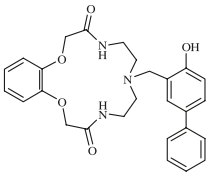
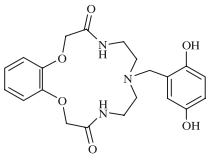
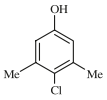
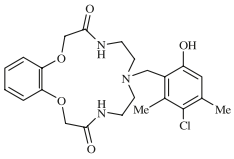
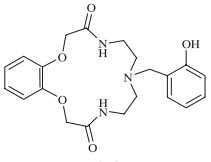


8 **9–19**

the reaction was completed. The product was isolated by simple extraction of the solid mass by acetone followed by the usual workup.

To investigate the generality and versatility of this method, the reaction was extended to various structurally diverse phenols. When the phenols had either electron-donating or electron-withdrawing substituents, the formation of benzylamine bonds occurred very rapidly, within 20–30 min. The results of the Mannich reaction of azacrown ether **8** are collected in Table 1. When *para*-substituted or

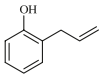
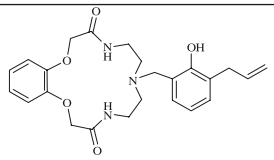
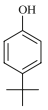
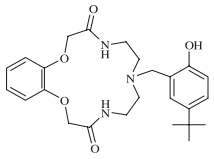
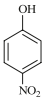
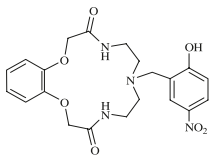
Table 1 (*continued*).

Entry	Substrate	Phenols	Product	Yield (%)
8	**8**		 **10**	73
9	**8**		 **11**	75
10	**8**		 **12**	81
11	**8**		 **13**	79
12	**8**		 **14**	71
13	**8**		 **15**	79
14	**8**		 **16**	78

unsubstituted phenols were used for the Mannich reaction with azacrown ether **8** in the presence of paraformaldehyde, macrocyclic ligands **9**–**19** were obtained in relatively high yields (Table 1, entries 7–17), although the yields drop as strongly electron-withdrawing substituents are added, as in **19** (Table 1, entry 17). The moderate yield of **19** is attributed to the relatively weak nucleophilicity of *p*-nitrophenol and its anion (14b). Aminomethylation of phenols by means of the Mannich reaction usually occurs in the position ortho to the phenolic OH group even if the para position is unsubstituted (14a). Possibly the preferential attack on the ortho position is caused by formation of a six-membered transition state where the phenolic proton activates the aminomethylating reagent (17). The free para positions on the benzo units of the final macrocycles are attractive sites for functionalization because of their high reactivity toward electrophilic aromatic substitution.

Additionally a variety of secondary amines were examined using *p*-cresol as the model substrate (Table 1). Interestingly the yield of the reaction was higher when graphite was used as the reaction medium than when the reaction was performed in benzene. For example, with graphite, the reac-

Table 1 (*concluded*).

Entry	Substrate	Phenols	Product	Yield (%)
15	**8**		 **17**	74
16	**8**		 **18**	72
17	**8**		 **19**	40

tion of piperazine with *p*-cresol occurred in 85% yield after 20 min at 100 °C. Under reflux conditions in benzene, the same reaction was slower, and afforded the corresponding product only after 24 h in 41% yield (Table 1, entry 4) (14*d*).

Further, the activity of the recovered graphite was examined. As shown in Table 2, the yields of macrocyclic **9** in the second and third uses of the graphite was almost same as that in the first use. In every case >90% of the graphite was easily recovered from the reaction mixture by simple washing with acetone.

A comparison of the present protocol, using graphite, with selected previously known protocols and other inorganic solids that were examined is collected in Table 3 to demonstrate that the present protocol is indeed superior to several of the other protocols. According to Table 3, the Mannich reaction of azacrown ether **8** is completed in 20 min at 100 °C in 87% isolated yield using the present protocol. Most of the other protocols listed either take a longer time for completion, or use toxic solvents with generally reduced isolated yields (entries 1–6) (14). In another study the effect of microwave and inorganic solids as catalysts were investigated and it was found that compound **9** was not produced under these conditions (entry 7, 8, 9) (18, 19, 20). In the absence of graphite (entry 10), the reaction was conducted at 100 °C for 2 h, affording compound **9** only, in 30% yield. The effect of different amounts of graphite on the model compound was studied in another experiment. The result showed that the best yield was obtained when 1 gr of graphite was used. Increasing the amount of graphite had a negligible effect on the efficiency of the reaction. Decreasing the amount of graphite led to a pasty reaction mixture which made the stirring difficult, thus reducing the efficiency of the model reaction.

The Mannich reaction of azacrown ether **8** with *p*-cresol on a 30 mmol scale proceeded just as well as the 1 mmol reaction. The mechanism of the reaction is a subject of a further study. For now, we believe that graphite acts as a dehydration reagent or as a heat-conducting surface for the Mannich reaction.

Table 2. Re-use of graphite.

Number of uses	Yield (%)[a]	Recovery of graphite
1	87	95
2	83	92
3	80	91

[a]Isolated yields.

At the edge of the basal planes of carbon atoms in the graphite structure, where bonding in the plane is terminated, are unsaturated carbon atoms. These sites are associated with high concentrations of unpaired electrons and therefore play a significant role in chemisorption. These carbons may chemisorb oxygen, producing oxygen surface groups. Oxygen surface groups are by far the most important in influencing the surface characteristics and adsorption behavior of graphite (21) (Scheme 2).

The surface groups most often suggested are carboxyl, phenolic hydroxyl, and quinone carbonyl groups. Slightly fewer in number are the reports of ethers, peroxides, ester groups, lactones, carboxylic acid anhydrides, and cyclic peroxides (22). These structures exhibit a high affinity for water (23). As Szymanski et al. reported earlier, the dehydration of secondary alcohols on the carbon catalysts proceeds according to the oxonium mechanism (11*b*).

As described in Scheme 3, we have suggested a mechanism for the solvent-free Mannich reaction of secondary amines that is based on the previously proposed mechanism for dehydration of secondary alcohols.

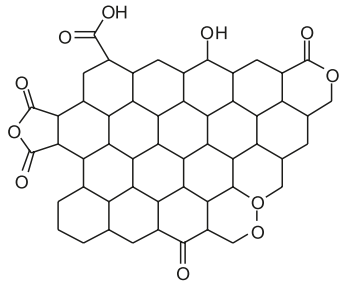
At the initial stage, the formaldehyde is protonated; then, a secondary amine attacks the activated formaldehyde; finally, a water molecule is lost from the oxonium intermediate (**II**) and the Mannich base (**III**) is formed. The reaction of Mannich base (**III**) with phenol gives the product.

Table 3. Mannich reaction of azacrown ether **8** with *p*-cresol under various conditions.

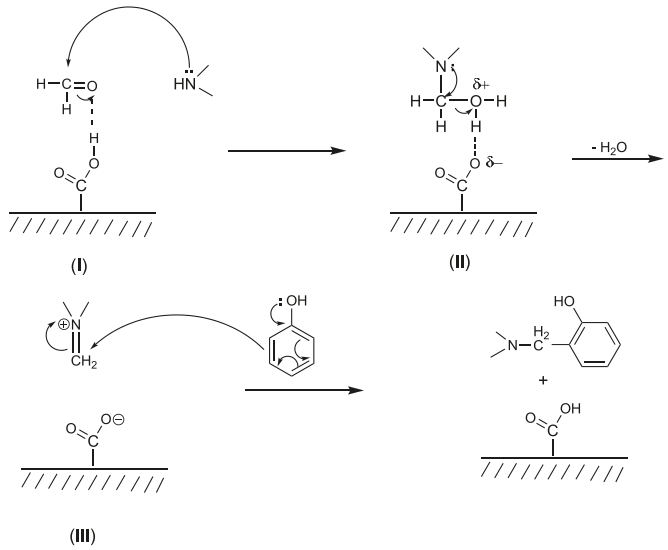
Entry	Condition	Temp. (°C)	Time	Yield (%)[a]
1	Benzene (14*b*)	reflux	2 h	10
2	Benzene/graphite	reflux	2 h	20
3	CCl_4 (14*a*)	reflux	2 h	7
4	CCl_4/graphite	reflux	2 h	12
5	Toluene (14*c*)	reflux	2 h	15
6	Toluene/graphite	reflux	2 h	22
7	Al_2O_3/MW (18)		1.5 min	no reaction
8	Al_2O_3/CH_3SO_3H (AMA) (19)	100	2 h	no reaction
9	Graphite/CH_3SO_3H (GMA) (20)	100	2 h	no reaction
10	Neat	100	2 h	30
11	Graphite	70	3600 min	81
12	Graphite	100	20 min	87
13	Graphite	130	6 min	85

[a]Isolated yields.

Scheme 2. Some type of oxygen surface groups in graphite.



Scheme 3.



Conclusion

We have described a novel and highly efficient solvent-free protocol for the Mannich reaction of phenol compounds using nontoxic and inexpensive graphite 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, short reaction times, reusability of graphite, and the elimination of solvents.

Experimental

Instrumentation, analysis, and starting material

NMR spectra were recorded on Bruker Avance DPX-250 (^{1}H NMR 250 MHz and ^{13}C NMR 62.9 MHz) and DRX-500 (^{19}F NMR 470 MHz) spectrometers in pure deuterated solvents with tetramethylsilane (TMS) and trichlorofluoromethane ($CFCl_3$) as internal standards. Infrared spectra were obtained using a Shimadzu FT-IR 8300 spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 or 20 ev. Melting points were determined in open capillary tubes in a Buchi-535 circulating oil melting point apparatus. UV–vis spectra were 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, Sigma-Aldrich, and Merck Companies.

General procedure

After a mortar was charged with azacrown ether **8** (1 mmol), phenol (1.2 mmol), paraformaldehyde (1.2 mmol), and graphite slurry (1 g) (CAS No.7782–42–5; fine powder extra pure, particle size (<50 μm), pH value 5–6 (50 g/l, H_2O, 20 °C) from Merck), the mixture was ground with a pestle at room temperature. The resulting fine powder was transferred to a round-bottomed flask and stirred on a magnetic stirrer in an oil bath at 100 °C for 20–30 min. After cooling, acetone (3 × 25 mL) was added to the mixture and the graphite was removed by filtration. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromathography

(eluent: n-hexane – ethyl acetate 1:1) or recrystallized from ethyl acetate.

4-Methyl-2-(1-piperidinylmethyl)phenol (1)

Purification by plate chromatography, eluted with n-hexane – ethyl acetate (10:2), gave compound **1** in 90% yield; mp 45 °C (Lit. Value: 45 °C (24)). IR (KBr, cm^{-1}) υ_{max} : 3240, 2935, 2804, 1601, 1497, 1338, 1308, 1038, 814, 791, 771. ^1H NMR ($CDCl_3$) δ_H: 10.90 (1H, s), 6.82 (1H, d, J = 8.2 Hz), 6.58 (1H, s), 6.52 (1H, d, J = 8.2 Hz), 3.40 (2H, s), 2.17–2.36 (4H, m), 2.11 (3H, s), 1.17–1.54 (6H, m). ^{13}C NMR ($CDCl_3$) δ_C: 155.7, 129.1, 128.9, 128.2, 121.3, 115.7, 62.2, 54.2, 25.7, 24.3, 20.9. Anal. calcd.. for $C_{13}H_{19}NO$: C 76.06, H 9.33; found: C 76.27, H 9.12.

4-Methyl-2-(4-morpholinylmethyl)phenol (2)

Purification by plate chromatography, eluted with n-hexane – ethyl acetate (10:2), gave compound **2** in 96% yield; mp 49–50 °C (Lit. Value: 48–51 °C (25)). IR (neat, cm^{-1}) υ_{max}: 3160, 2819, 1597, 1304, 1119, 1029, 818. ^1H NMR ($CDCl_3$) δ_H: 9.28 (1H, s), 6.77 (1H, d, J = 7.8 Hz), 6.58 (1H, s), 6.47 (1H, d, J = 7.8 Hz), 3.48 (4H, t, J = 4.2 Hz), 3.40 (2H, s), 2.29 (4H, s), 2.06 (3H, s). ^{13}C NMR ($CDCl_3$) δ_C: 154.5, 128.9, 128.1, 120.4, 116.3, 115.8, 66.6, 61.3, 52.8, 20.7. Anal. calcd. for $C_{12}H_{17}NO_2$: C 69.54, H 8.27; found: C 69.36, H, 8.49.

2-{[Bis(2-hydroxyethyl)amino]methyl}-4-methylphenol (3)

Purification by plate chromatography, eluted with n-hexane – ethyl acetate (10:2), gave compound **3** in 82% yield. (Lit. values, see ref. 26). IR υ_{max} (neat, cm^{-1}): 3356, 2870, 1612, 1481, 1304, 1038, 910, 817, 733. ^1H NMR ($CDCl_3$) δ_H: 6.59–7.05 (5H, m), 3.72 (2H, s), 3.61 (4H, t, J = 5.4 Hz), 2.67 (4H, t, J = 5.4 Hz), 2.14 (3H, s). ^{13}C NMR ($CDCl_3$) δ_C: 154.4, 130.5, 129.1, 122.2, 116.7, 115.5, 58.9, 58.0, 52.8, 20.9. MS *m/z* (%): 227 ([M^+ + 2], 0.1), 226 ([M^+ + 1], 0.5), 225 ([M^+], 1.7), 208 (0.3), 194 (11.6), 162 (1.1), 149 (1.1), 135 (1.4), 121 (34.2), 91 (13.1), 84 (57.4), 74 (100). Anal. calcd. for $C_{12}H_{19}NO_3$: C 63.98, H 8.50; found: C 63.79, H 8.44.

2-{[4-(2-Hydroxy-5-methylbenzyl)-1-piperazinyl]methyl}-4-methylphenol (4)

Rrecrystallization from MeOH gave compound **4** as a colorless powder in 85% yield; mp 225–226 °C (Lit. Value: 225–226 °C (14*d*)). ^1H NMR ($CDCl_3$) δ_H: 10.22 (2H, s), 6.89 (2H, d, J = 8.2 Hz), 6.69 (2H, s), 6.64 (2H, d, J = 8.2 Hz), 3.58 (4H, s), 3.23–2.31 (8H, m), 2.15 (6H, s). ^{13}C NMR ($CDCl_3$) δ_C: 155.1, 129.3, 128.3, 120.5, 115.8, 61.2, 52.4, 20.5. Anal. calcd. for $C_{20}H_{26}N_2O_2$: C 73.59, H 8.03; found: C 73.82, H 7.79.

2-{[16-(2-Hydroxy-5-methylbenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl]methyl}-4-methylphenol (5)

Purification by flash column chromatography, eluted with n-hexane – ethyl acetate (1:1), gave compound **5** as a colorless powder in 88% yield; mp 113–114 °C (Lit. Value: 114–115 °C (14*b*)). ^1H NMR ($CDCl_3$) δ_H: 6.95 (2H, d, J = 8.2 Hz), 6.72 (2H, d, J = 8.2 Hz), 6.78 (2H, s), 3.77 (4H, s), 3.66 (8H, t, J = 5.4 Hz), 3.61 (8H, s), 2.86 (8H, t, J = 5.4 Hz), 2.23 (6H, s). ^{13}C NMR ($CDCl_3$) δ_C: 155.5, 129.3, 129.1, 122.1, 116.0, 70.7, 69.1, 58.6, 53.6, 20.5. Anal. calcd. for $C_{28}H_{42}N_2O_6$: C 66.91, H 8.42; found: C 66.89, H 8.61.

5,6,7,8,9,10,11,12-Octahydro-2*H*-1,15,4,8,12-benzodioxatriazacycloheptadecine-3,13(4*H*,14*H*)-dione (6)

Rrecrystallization from toluene gave compound **6** as a colorless powder in 70% yield; mp 186 °C (Lit. Value: 187 °C (27)). IR (KBr, cm^{-1}) υ_{max}: 3437, 2924, 2839, 1686, 1543, 1504, 1450, 1254, 1215, 1130, 1049, 818, 760, 582. ^1H NMR ($CDCl_3$) δ_H: 7.46 (2H, s), 6.98–6.84 (4H, m), 4.48 (4H, s), 3.52 (4H, q, J = 6.0 Hz), 2.64 (4H, t, J = 5.7 Hz), 1.78–1.71 (4H, m), 1.04 (1H, br). ^{13}C NMR ($CDCl_3$) δ_C: 167.9, 147.0, 122.7, 113.6, 67.9, 47.2, 36.8, 27.7. MS *m/z* (%): 323 ([M^+ + 2], 5.0), 322 ([M^+ + 1], 26.1), 321 ([M^+], 5.0), 263 (10.3), 236 (7.4), 220 (5.6), 208 (3.4), 180 (3.5), 163 (4.0), 155 (18.9), 135 (10.7), 127 (13.2), 113 (22.1), 100 (24.9), 85 (44.7), 70 (42.1), 56 (70.8), 44 (100). Anal. calcd. for $C_{16}H_{23}N_3O_4$: C 59.80, H 7.21; found: C 59.68, H 7.34.

8-(2-Hydroxy-5-methylbenzyl)-5,6,7,8,9,10,11,12-octahydro-2*H*-1,15,4,8,12-benzodioxatriazacycloheptadecine-3,13(4*H*,14*H*)-dione (7)

Purification by flash column chromatography, eluted with n-hexane – ethyl acetate (1:1), gave compound **7** as a colorless powder in 84% yield; mp 167 °C. IR (KBr, cm^{-1}) υ_{max}: 3329, 2962, 1662, 1550, 1504, 1450, 1254, 1126, 1041, 818, 752. ^1H NMR ($CDCl_3$) δ_H: 7.26 (2H, s), 7.04–6.93 (6H, m), 6.76 (1H, d, J = 8.4 Hz), 4.56 (4H, s), 3.77 (2H, s), 3.42 (4H, q, J = 6.0 Hz), 2.66 (4H, t, J = 5.7 Hz), 2.28 (3H, s), 1.86–1.73 (4H, m). ^{13}C NMR ($CDCl_3$) δ_C: 168.1, 155.2, 147.0, 129.5, 129.2, 123.1, 122.0, 115.9, 114.6, 68.5, 58.1, 50.9, 36.2, 26.0, 20.4. MS *m/z* (%): 334 ([M^+ – 107], 1.2), 333 (9.2), 332 (6.7), 303 (0.5), 291 (1.1), 290 (5.0), 275 (3.9), 261 (2.0), 247 (6.2), 225 (3.4), 220 (3.0), 210 (3.4), 208 (3.6), 183 (12.6), 168 (15.29), 153 (14.8), 140 (28.7), 121 (28.9), 111 (28.7), 98 (62.4), 84 (46.7), 70 (81.4), 56 (100). Anal. calcd. for $C_{24}H_{31}N_3O_5$: C 65.29, H 7.08; found: C 65.84, H 6.87.

7-(2-Hydroxy-5-methylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (9)

Purification by flash column chromatography, eluted with n-hexane – ethyl acetate (1:1), gave compound **9** as a colorless powder in 87% yield; mp 206 °C. UV–vis (chloroform, nm, (logϵ)) λ_{max}: 271 (3.33), 244 (3.04). IR (KBr, cm^{-1}) υ_{max}: 3400, 3200, 2900, 2860, 2680, 1662, 1598, 1540, 1506, 1438, 1259, 1215, 1047, 1128, 815, 740. ^1H NMR ($CDCl_3$) δ_H: 8.14 (1H, s), 7.56 (2H, s), 7.07–6.87 (6H, m), 6.64 (1H, d, J = 8.0 Hz), 4.51 (4H, s), 3.73 (2H, s), 3.54 (4H, t, J = 5.3 Hz), 2.75 (4H, t, J = 5.3 Hz), 2.22 (3H, s). ^{13}C NMR ($CDCl_3$) δ_C: 168.3, 154.0, 147.6, 131.0, 130.0, 129.5, 123.2, 122.4, 116.1, 114.9, 68.7, 56.0, 53.3, 36.2, 20.8. 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 $C_{22}H_{27}N_3O_5$: C 63.91, H 6.58; found: C 63.75, H 6.43.

7-(5-Bromo-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (10)

Rrecrystallization from EtOAc gave compound **10** as a colorless powder in 73% yield; mp 238 °C (decomposed). UV–vis (chloroform, nm (logϵ)) λ_{max}: 374 (1.81), 269 (3.22), 246 (3.08) IR (KBr, cm^{-1}) υ_{max} : 3393, 3200, 2900, 1663, 1590, 1542, 1502, 1464, 1425, 1370, 1258, 1218, 1128, 1106, 1056, 823, 750. ^{1}H NMR (DMSO-d_6) δ_H: 9.81 (1H, s), 7.80 (2H, s), 7.38 (1H, d, J = 1.9 Hz), 7.12–6.95 (5H, m), 6.68 (1H, d, J = 8.6 Hz), 4.44 (4H, s), 3.54 (2H, s), 3.40 (4H, t, J = 5.3 Hz), 2.64 (4H, t, J = 5.3 Hz). ^{13}C NMR (DMSO-d_6) δ_C: 167.2, 155.2, 147.2, 132.3, 130.5, 127.6, 122.2, 117.3, 114.4, 110.3, 68.0, 52.2, 50.1, 35.4. MS *m/z* (%): 479 ([M^+ + 2], 1.5), 477 ([M^+], 1.5), 407 (2.0), 405 (2.0), 292 (29.3), 242 (10.2), 240 (10.2), 225 (27.4), 206 (10.5), 187 (13.4), 185 (13.4), 167 (12.6), 150 (12.5), 121 (22.2), 85 (59.3), 56 (100.0), 43 (89.2). Anal. calcd. for $C_{21}H_{24}BrN_3O_5$: C 52.73, H 5.06; found: C 52.85, H 4.88.

7-(5-Chloro-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (11)

Recrystallization from EtOAc gave compound **11** as a colorless powder in 75% yield; mp 237 °C (decomposed). UV–vis (chloroform, nm (logϵ)) λ_{max}: 360 (2.97), 292 (3.25), 272 (3.24), 246 (3.13). IR (KBr, cm^{-1}) υ_{max}: 3394, 3250, 2950, 2850, 1662, 1590, 1540, 1500, 1427, 1370, 1245, 1210, 1128, 1056, 823, 756, 653. ^{1}H NMR (DMSO-d_6) δ_H: 9.78 (1H, s), 7.80 (2H, s), 7.27 (1H, d, J = 2.2 Hz), 6.95–7.11 (5H, m), 6.72 (1H, d, J = 8.6 Hz), 4.44 (4H, s), 3.54 (2H, s), 3.40 (4H, t, J = 5.3 Hz), 2.64 (4H, t, J = 5.3 Hz). ^{13}C NMR (DMSO-d_6) δ_C: 167.2, 154.8, 147.2, 129.5, 127.6, 127.0, 122.7, 122.2, 116.8, 114.4, 68.0, 52.2, 50.1, 35.4. 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 $C_{21}H_{24}ClN_3O_5$: C 58.13, H 5.58; found: C 57.89, H 5.76.

7-(5-Fluoro-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (12)

Purification by flash column chromatography, eluted with n-hexane – ethyl acetate (1:1), gave compound **12** as a colorless powder in 81% yield; mp 214 °C. UV–vis (chloroform, nm (logϵ)) λ_{max} : 288 (3.21), 270 (3.22), 245 (2.73). IR (KBr, cm^{-1}) υ_{max}: 3404, 3078, 2916, 2822, 1676, 1549, 1506, 1448, 1259, 1219, 1195, 1130, 1057, 818, 748. ^{1}H NMR ($CDCl_3$) δ_H: 8.55 (1H, s), 7.46 (2H, s), 7.06–6.91 (4H, m), 6.87–6.63 (3H, m), 4.51 (4H, s), 3.74 (2H, s), 3.54 (4H, t, J = 5.3 Hz), 2.75 (4H, t, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$) δ_C: 168.1, 158.2, 154.5, 152.1, 147.2, 122.9, 116.8, 116.3, 115.9, 114.8, 68.5, 56.0, 52.8, 35.7. ^{19}F NMR ($CDCl_3$) δ_F: –125.0 (1F). MS *m/z* (%): 418 ([M^+ + 1], 1.0), 417 ([M^+], 2.5), 400 (0.2), 346 (0.2), 345 (3.0), 294 (0.8), 293 (3.8), 292 (19.2), 225 (29.7), 206 (14.1), 180 (31.1), 167 (28.1), 150 (16.7), 125 (36.2), 96 (38.1), 85 (49.0), 69 (50.2), 56 (100). Anal. calcd. for $C_{21}H_{24}FN_3O_5$: C 60.42, H 5.80; found: C 60.57. H 5.74.

7-[(4-Hydroxy[1,1'-biphenyl]-3-yl)methyl]-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (13)

Recrystallization from EtOAc gave compound **13** as a colorless powder in 79% yield; mp 190 °C. UV–vis (chloroform, nm (logϵ)) λ_{max}: 293 (3.28), 253 (3.36). IR (KBr, cm^{-1}) υ_{max}: 3380, 3250, 3030, 2950, 2850, 1672, 1598, 1540, 1506, 1456, 1264, 1225, 1127, 1049, 752. ^{1}H NMR ($CDCl_3$) δ_H: 8.81(1H, s), 7.61 (2H, s), 7.48–7.01 (8H, m), 6.90–6.82 (4H, m), 4.47 (4H, s), 3.82 (2H, s), 3.55 (4H, t, J = 5.3 Hz), 2.78 (4H, t, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$) δ_C: 168.4, 156.0, 147.4, 141.0, 133.4, 129.2, 129.0, 128.1, 127.0, 126.9, 123.0, 116.6, 114.6, 68.4, 54.6, 53.3, 36.2. MS *m/z* (%): 477 ([M^+ + 2], 0.1), 476 ([M^+ + 1], 0.4), 475 ([M^+], 1.0), 403 (1.0), 368 (0.4), 352 (1.1), 313 (0.3), 293 (5.5), 249 (5.3), 225 (68.2), 182 (18.1), 167 (23.4), 150 (21.5), 121 (22.8), 113 (22.9), 85 (47.0), 69 (100.0), 56 (89.7), 43 (87.6). Anal. calcd. for $C_{27}H_{29}N_3O_5$: C 68.19, H 6.15; found: C 68.35, H 6.28.

7-(2,5-Dihydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (14)

Recrystallization from EtOAc gave compound **14** as a colorless powder in 71% yield; mp 170 °C. UV–vis (DMSO, nm (logϵ)) λ_{max}: 301 (3.42), 279 (3.41). IR (KBr,cm^{-1}) υ_{max}: 3394, 2916, 2825, 1663, 1597, 1541, 1504, 1259, 1213, 1126, 1051, 818, 750. ^{1}H NMR (DMSO-d_6) δ_H: 8.71 (1H, s), 8.46 (1H, s), 7.67 (2H, s), 7.04–6.88 (4H, m), 6.47–6.32 (3H, m), 4.37 (4H, s), 3.45 (2H, s), 3.31 (4H, t, J = 5.3 Hz), 2.54 (4H, t, J = 5.3 Hz). ^{13}C NMR (DMSO-d_6) δ_C: 166.9, 149.3, 148.5, 146.5, 123.3, 121.8, 117.2, 115.6, 114.4, 114.0, 67.6, 51.5, 49.9, 35.0. MS *m/z* (%): 416 ([M^+ + 1], 0.2), 294 (1.9), 293 (2.6), 292 (0.7), 249 (5.1), 225 (51.3), 180 (13.3), 167 (18.6), 150 (17.3), 123 (25.6), 121 (23.5), 99 (17.7), 85 (42.4), 69 (83.7), 56 (100). Anal. calcd. for $C_{21}H_{25}N_3O_6$: C 60.71, H 6.07; found: C 60.53, H 5.89.

7-(3-Chloro-6-hydroxy-2,4-dimethylbenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (15)

Recrystallization from EtOAc gave compound **15** as a colorless powder in 79% yield; mp 241 °C (decomposed). UV–vis (chloroform, nm (logϵ)) λ_{max}: 271 (3.21), 246 (3.15). IR (KBr, cm^{-1}) υ_{max}: 3375, 3190, 2878, 2806, 1657, 1599, 1541, 1506, 1438, 1211, 1122, 1063, 815, 744. ^{1}H NMR ($CDCl_3$) δ_H: 9.43 (1H, s), 7.41 (2H, s), 7.07–6.91 (4H, m), 6.50 (1H, s), 4.51 (4H, s), 3.83 (2H, s), 3.54 (4H, t, J = 5.3 Hz), 2.75 (4H, t, J = 5.3 Hz), 2.33 (3H, s), 2.26 (3H, s). ^{13}C NMR ($CDCl_3$) δ_C: 168.1, 154.8, 147.3, 139.0, 136.8, 123.0, 118.9, 116.1, 115.1, 68.6, 53.8, 52.8, 35.8, 21.1, 16.9. 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 $C_{23}H_{28}ClN_3O_5$: C 59.80, H 6.11; found: C 59.95, H 6.01.

7-(2-Hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (16)

Purification by flash column chromatography, eluted with n-hexane – ethyl acetate (1:1), gave compound **16** as a colorless powder in 78% yield; mp 190 °C. UV–vis (chloroform, nm (logϵ)) λ_{max}: 267 (3.24), 245 (2.85). IR (KBr, cm^{-1}) υ_{max}: 3398, 3074, 2893, 2849, 1661, 1593, 1504, 1456, 1439, 1257, 1219, 1130, 1061, 818, 744. ^{1}H NMR ($CDCl_3$) δ_H: 8.56 (1H, s), 7.55 (2H, s), 7.14–6.70 (8H, m), 4.48 (4H, s), 3.75 (2H, s), 3.51 (4H, t, J = 5.3 Hz), 2.74 (4H, t, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$) δ_C: 168.0, 156.0, 147.2, 130.1, 129.2, 122.8, 122.1, 119.9, 115.8, 115.4, 114.5, 68.3, 55.4, 52.8, 35.8. MS *m/z* (%): 401 ([M^+ + 2], 0.1), 400 ([M^+ + 1], 0.9), 399 ([M^+], 0.9), 328 (0.9), 327 (6.3), 294 (1.9), 293 (4.6), 292 (18.5), 225 (20.5), 162 (18.8), 148 (18.6), 121 (21.8), 107 (57.7), 85 (55.0), 56 (100). Anal. calcd. for $C_{21}H_{25}N_3O_5$: C 63.14, H 6.31; found: C 62.98, H 6.45.

7-(3-Allyl-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (17)

Rrecrystallization from EtOAc gave compound **17** as a colorless powder in 74% yield; mp 188 °C. UV–vis (chloroform, nm (logϵ)) λ_{max}: 282 (3.20), 265 (3.26), 246 (3.06). IR (KBr, cm^{-1}) υ_{max}: 3304, 2914, 2824, 1662, 1596, 1545, 1504, 1458, 1439, 1261, 1148, 1121, 1047, 812, 752. ^{1}H NMR ($CDCl_3$) δ_H: 8.89 (1H, s), 7.49 (2H, s), 7.05–6.87 (6H, m), 6.72 (1H, t, J = 7.5 Hz), 5.85–5.69 (1H, m), 4.85 (1H, dd, J = 10, 1.65 Hz), 4.78 (1H, dd, J = 17 Hz, 1.72 Hz), 4.48 (4H, s), 3.74 (2H, s), 3.51 (4H, t, J = 5.3 Hz), 3.12 (2H, d, J = 6.5 Hz), 2.73 (4H, t, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$) δ_C: 168.1, 154.2, 147.3, 136.7, 129.7, 127.6, 126.4, 122.9, 121.7, 119.6, 115.5, 114.9, 68.5, 57.1, 52.6, 35.6, 34.1. MS *m/z* (%): 440 ([M^+ + 1], 1.6), 439 ([M^+], 3.8), 368 (1.9), 367 (6.6), 294 (4.4), 293 (6.4), 292 (25.1), 226 (4.0), 225 (30.2), 206 (10.1), 202 (13.8), 188 (19.3), 167 (14.5), 147 (43.6), 131 (25.1), 117 (25.5), 91 (51.4), 85 (62.2), 69 (63.9), 56 (100). Anal. calcd. for $C_{24}H_{29}N_3O_5$: C 65.59, H 6.65; found: C 65.41, H 6.78.

7-(5-*tert*-Butyl-2-hydroxybenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (18)

Rrecrystallization from EtOAc gave compound **18** as a colorless powder in 72% yield; mp 216 °C. UV–vis (chloroform, nm (logϵ)) λ_{max}: 282 (3.19), 267 (3.23), 245 (2.96). IR (KBr, cm^{-1}) υ_{max}: 3377, 3281, 2955, 2906, 1676, 1597, 1539, 1506, 1439, 1346, 1263, 1225, 1128, 1051, 820, 725. ^{1}H NMR ($CDCl_3$) δ_H: 8.44 (1H, s), 7.62 (2H, s), 7.11 (1H, d, J = 8.4 Hz), 7.04 (1H, s), 7.01–6.84 (4H, m), 6.68 (1H, d, J = 8.4 Hz), 4.44 (4H, s), 3.73 (2H, s), 3.52 (4H, t, J = 5.3 Hz), 2.74 (4H, t, J = 5.3 Hz), 1.23 (9H, s). ^{13}C NMR ($CDCl_3$) δ_C: 167.9, 153.6, 147.0, 142.5, 127.1, 125.8, 122.6, 121.4, 115.2, 114.1, 68.0, 54.8, 52.4, 35.7, 33.9, 31.5. 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 $C_{25}H_{33}N_3O_5$: C 65.91, H 7.30; found: C 66.07, H 7.41.

7-(2-Hydroxy-5-nitrobenzyl)-5,6,7,8,9,10-hexahydro-2*H*-1,13,4,7,10-benzodioxatriazacyclopentadecine-3,11(4*H*,12*H*)-dione (19)

Rrecrystallization from EtOAc gave compound **19** as yellow powder in 40% yield; mp 239.5 °C (decomposed). UV–vis (DMSO, nm (logϵ)) λ_{max}: 354 (3.43), 298 (3.45). IR (KBr, cm^{-1}) υ_{max}: 3390, 3200, 2850, 1667, 1600, 1550, 1530, 1500, 1440, 1335, 1295, 1257, 1218, 1128, 1085, 1056, 830, 817, 750. ^{1}H NMR (DMSO-d_6) δ_H: 8.11 (1H, d, J = 2.2 Hz), 7.95 (1H, dd, J = 8.9, 2.3 Hz), 7.80 (2H, s), 7.11–6.96 (4H, m), 6.89 (1H, d, J = 8.9 Hz), 4.40 (4H, s), 3.65 (2H, s), 3.37 (4H, t, J = 5.3 Hz), 2.51 (4H, t, J = 5.3 Hz). ^{13}C NMR (DMSO-d_6) δ_C: 167.4, 162.6, 147.4, 139.7, 126.6, 126.3, 126.0, 124.7, 122.4, 115.6, 114.7, 68.3, 52.4, 50.6, 35.5. 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 $C_{21}H_{24}N_4O_7$: C 56.75, H 5.44; found: C 56.58, H 5.26.

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