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Synthesis and Antimicrobial Evaluation of Tricyclic Macrocycles Containing a Chalcone Moiety[1]

A. Dongamanti*, V. K. Aamate, S. Gundu, and M. G. Devulapally

Department of Chemistry, Osmania University, Hyderabad, 500007 India
**e-mail: ashokdou@gmail.com*

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Abstract—A series of new tricyclic macrocycles containing a chalcone moiety were synthesized from chalcones through alkylation using different dibromoalkanes. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data and evaluated for their in vitro antimicrobial activity.

Keywords: chalcones, macrocycles, antimicrobial activity
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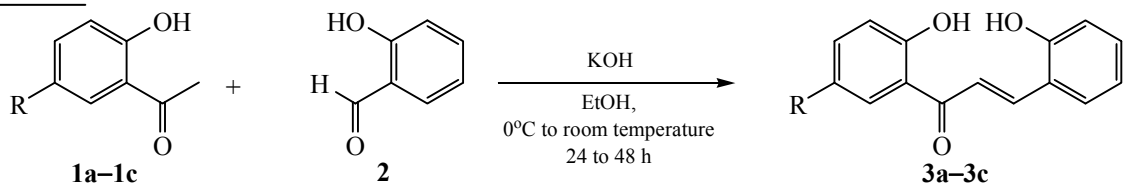
Macrocyclic ring structures are known for their capability of extremely potent biological activity and specificity. Their structural preorganization enables them to reduce the entropy cost of receptor binding compared to linear analogs [1, 2]. Numerous reports are known on the biological significance of macrocycles in the literature [3–5]. Therefore, increasing interest has been dedicated to the synthesis of macrocyclic structural frameworks. Chalcones are the biogenetic precursors of flavonoids [6], which is the main reason for the growing importance of such class of compounds. Chalcones exhibit a broad spectrum of biological activities, specifically anti-inflammatory [7], antiviral [8], antioxidant [9], anticancer [10], and antimalarial [11]. Therefore, the synthesis of diverse classes of compounds containing a chalcone moiety has attracted particular interest of researchers.

Inspired by the above observations and in continuation to our ongoing efforts in exploiting the biological properties of macrocyclic structural frameworks incorporated with heterocycles [12], we have designed a simple synthesis for the construction of tricyclic macrocycles containing a chalcone moiety and further evaluated their antimicrobial activity.

The required tricyclic scaffolds were synthesized in two stages. The first involved the Claisen–Schmidt condensation of substituted 2-hydroxyacetophenones **1a–1c** and salicylaldehyde **2** in the presence of potassium hydroxide to obtain the corresponding chalcones **3a–3c** [reaction (1)] [13–15]. At the second stage, chalcones **3a–3c** were treated with dibromoalkanes **4a–4d** in the presence of anhydrous potassium carbonate in DMF at 80°C for 8 h under a nitrogen atmosphere to form the required tricyclic compounds **5a–5l** in good yields [reaction (2)] [16].All the newly synthesized compounds were characterized by IR and NMR spectroscopy and mass spectrometry.

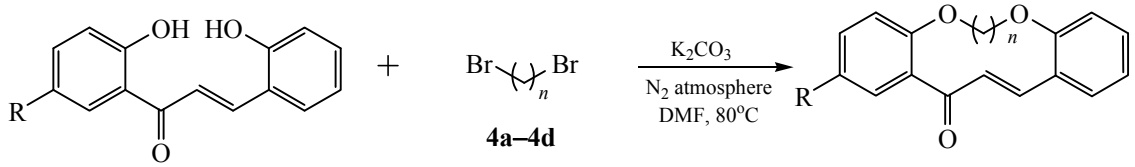


1a–1c + **2** → **3a–3c** (1)

R = H, Cl, F.

The synthesized compounds **5a–5l** were tested for their in vitro antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* at a concentration of 100 μg/mL, and the results of the antibacterial screening were compared with the standard antibacterial drug amoxicilin. The activity was studied using the cup plate agar diffusion method by measuring the zone of inhibition. The resulting values are listed in the table**.** As seen, compounds **5a**, **5b**, **5d**, **5e**, **5g**, **5i,** and **5j**

[1] The text was submitted by the authors in English.



3a–3c

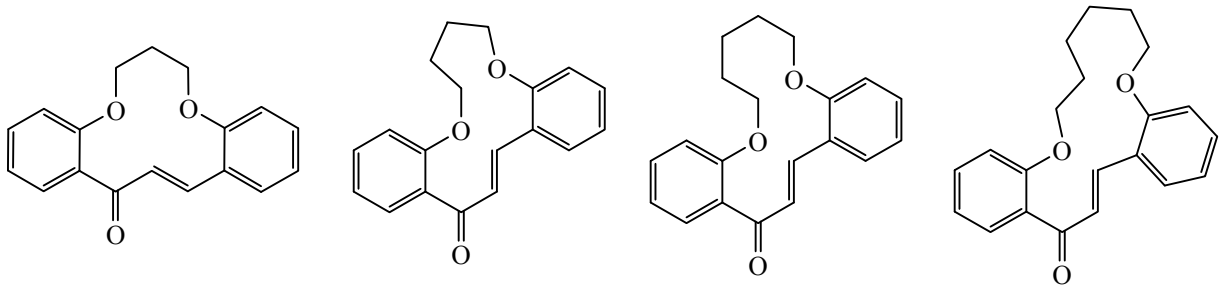
R = H, Cl, F

4a–4d

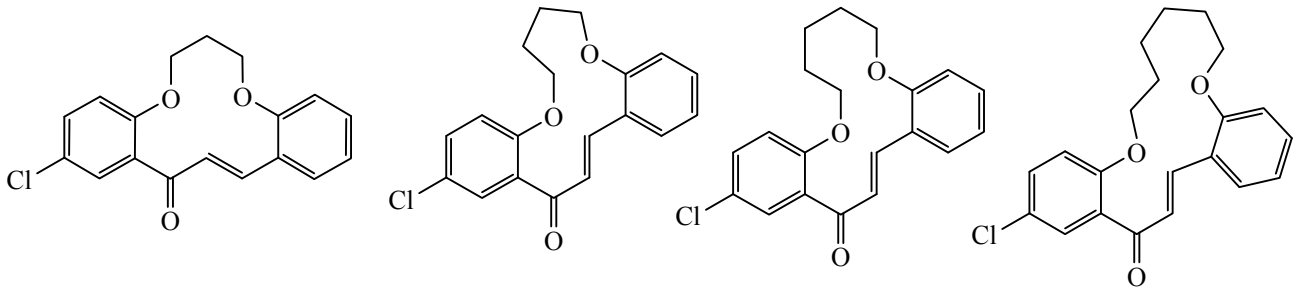
5a–5l

n = 3–6

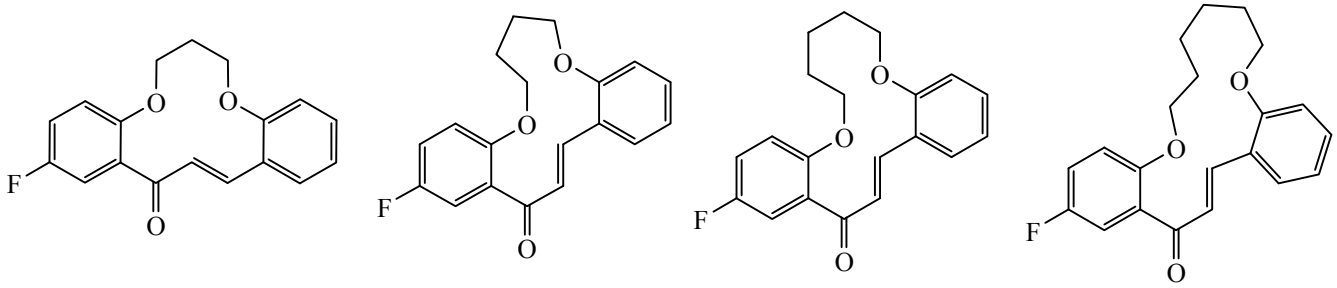
isolated yields 66–85%



5a **5b** **5c** **5d** (2)



5e **5f** **5g** **5h**



5i **5j** **5k** **5l**

displayed the highest inhibitory activity against *Bacillus subtilis,* compounds **5g** and **5h** showed good inhibitory activity against *Staphylococcus aureus* and *Escherichia coli,* and the highest inhibitory activity against *Pseudomonas aeruginosa* was characteristic of compounds **5a**, **5b**, **5g,** and **5i**.

Compounds **5a–5l** were also tested for their in vitro antifungal activity against *Aspergillus niger* and *Aspergillus flavus* at a concentration of 100 μg/mL, and the results of the antifungal screening were compared with the standard antifungal drug clotrimazole.The measured zones of inhibition are

Antimicrobial and antifungal activities of compounds **5a–5l**[a]

Compound	Zone of finhibition diameter, mm					
	bacteria				fungus	
	gram-positive		gram-negative		*A. niger*	*A. flavus*
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*		
5a	12	22	21	8	6.3	7.5
5b	11	23	19	7	8.6	3.8
5c	8	20	17	6	8.7	2.7
5d	14	15	9	5	8.6	8.7
5e	11	20	18	4	3.6	3.6
5f	10	22	21	2	14.6	13.4
5g	13	24	29	7	10.2	15.9
5h	9	26	25	3	16.5	4.6
5i	12	20	20	7	12.4	15.2
5j	11	18	18	5	4.6	8.4
5k	10	19	22	4	5.3	2.5
5l	8	16	21	2	10.4	6.3
Amoxicilin	13	29	31	9	–	–
Clotrimazole	–	–	–	–	17.3	16.7

[a] Concentration 100 μg/mL.

listed in the table. As seen, compounds **5f** and **5h** were the most efficient against *Aspergillus niger,* and compounds **5g** and **5i** exhibited a good inhibitory activity against *Aspergillus flavus.*

In summary, we have synthesized the titled tricyclic macrocycles in an easy synthetic strategy with good yields. All the products were evaluated for their in vitro antimicrobial activity, compounds **5a, 5b,** and **5d–5j** showed a good inhibitory efficiency against the test strains. Overall, the tricyclic macrocycles presented here could be an attractive template for the identification of novel antimicrobial agents.

EXPERIMENTAL

The reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light. Column chromategraphy was performed on silica gel (60–120 mesh) using distilled hexane and ethyl acetate. The melting points were determined in open glass capillary tubes on a Gallen–Kamp MFB-595 apparatus. The ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance II 400 MHz spectrometer in $CDCl_3$ solutions at 400 and 100 MHz, respectively. The proton chemical shifts were measured against internal TMS. The mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer. The IR spectra were recorded on a Shimadzu FT-IR-8400s spectrometer. Elemental analysis was performed on a Perkin Elmer CHN-2400 analyzer.

Synthesis of tricyclic macrocycles 5a–5l. A solution of compound (*E*)-1,3-bis(2-hydroxyphenyl)prop-2-en-1-one **3a–3c** (1 mmol) and anhydrous K_2CO_3 (5 mmol) in DMF was magnetically stirred at room temperature under nitrogen for 15 min. Dibromoalkane **4a–4d** (1 mmol) was then added, and the reaction mixture was stirred at 80°C for 12 h. The reaction completion was checked by TLC. The resulting solution was diluted with ice water and extracted with ethylacetate, the combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography to obtain the target macrocycles **5a–5l**.

7,8-Dihydrodibenzo[*f,k*][1,5]dioxacyclododecin-14(6*H*)-one (5a). Yield 85%. Light yellow solid; mp 96–98°C. IR spectrum, ν, cm^{-1}: 1625, 1616, 1454, 1294, 1280. ^1H NMR spectrum, δ, ppm: 2.23–2.29 m (2H), 4.14–4.17 t (*J* = 5.27 Hz, 2H), 4.39–4.41 t (*J* = 5.52 Hz, 2H), 7.07–7.17 m (4H, Ar-H), 7.28–7.32 m (1H, Ar-H), 7.34–7.37 d.d (*J* = 7.52 Hz, 1.75 Hz, 1H, Ar-H), 7.47–7.53 m (2H, Ar-H), 7.57–7.61 d (*J* = 16.06 Hz, 1H), 7.70–7.73 d.d (*J* = 7.52 Hz, 1.75 Hz, 1H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 29.4, 66.6, 69.3, 116.0, 120.4, 122.3, 123.8, 128.9, 130.3, 130.5, 130.7, 131.5, 132.6, 133.2, 138.2, 158.1, 158.2, 193.0. Found, %: C 77.05; H 5.82. $C_{18}H_{16}O_3$. Calculated, %: C 77.12; H 5.75. *M* 281.

8,9-Dihydro-6*H*-dibenzo[*g,l*][1,6]dioxacyclotridecin-15(7*H*)-one (5b). Yield 80%. Light yellow solid; mp 122–124°C. IR spectrum, ν, cm^{-1}: 1631, 1610, 1452, 1291, 1282. ^1H NMR spectrum, δ, ppm: 2.16–2.17 m (4H), 4.10–4.12 m (4H), 6.87–6.89 d (*J* = 8.03 Hz, 1H, Ar-H), 6.91–6.93 d (*J* = 8.03 Hz, 1H, Ar-H), 6.95–6.99 m (1H, Ar-H), 7.01–7.05 m (1H, Ar-H), 7.26–7.31 m (1H, Ar-H), 7.40–7.43 d.d (*J* = 7.52 Hz, 1.50 Hz, 1H, Ar-H), 7.44–7.49 m (1H, Ar-H), 7.61–7.65 d (*J* = 15.8 Hz, 1H), 8.06–8.09 d.d (*J* = 7.78 Hz, 2.0 Hz, 1H, Ar-H), 8.92–8.96 d (*J* = 15.8 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 25.9, 26.9, 68.3, 69.0, 111.6, 112.2, 120.6, 120.7, 124.5, 127.6, 130.4, 131.6, 132.0, 134.0, 134.3, 138.8, 159.0, 159.4, 190.5. Found, %: C 77.44; H 6.25. $C_{19}H_{18}O_3$. Calculated, %: C 77.53; H 6.16. *M* 295.

7,8,9,10-Tetrahydrodibenzo[*h,m*][1,7]dioxacyclotetradecin-16(6*H*)-one (5c). Yield 75%. Light yellow solid; mp 112–115°C. IR spectrum, ν, cm^{-1}: 1653, 1604, 1450, 1332, 1284. ^1H NMR spectrum, δ, ppm: 1.87–2.01 m (6H), 4.13–4.15 t (*J* = 4.76 Hz, 2H), 4.20–4.23 t (*J* = 5.52 Hz, 2H), 6.88–6.90 d (*J* = 8.28 Hz, 1H, Ar-H), 6.95–7.02 m (3H, Ar-H), 7.28–7.32 m (1H, Ar-H), 7.40–7.42 m (2H, Ar-H), 7.67–7.73 m (2H, Ar-H), 8.19–8.23 d (*J* = 15.8 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 21.1, 25.9, 26.6, 64.6, 68.2, 111.6, 112.2, 120.6, 120.7, 124.1, 129.7, 130.2, 130.8, 131.0, 132.9, 134.8, 139.6, 157.6, 159.4, 193.5. Found, %: C 77.96; H 6.60. $C_{20}H_{20}O_3$. Calculated, %: C 77.90; H 6.54. *M* 309.

8,9,10,11-Tetrahydro-6H-dibenzo[*i,n*][1,8]dioxacyclopentadecin-17(7*H*)-one (5d). Yield 68%. Light yellow solid; mp 102–104°C. IR spectrum, ν, cm^{-1}: 1635, 1611, 1448, 1304, 1285. ^1H NMR spectrum, δ, ppm: 1.63–1.71 m (4H), 1.81–1.85 m (4H), 4.15–4.18 t (*J* = 5.52 Hz, 2H), 4.26–4.28 t (*J* = 5.27 Hz, 2H), 6.92–7.01 m (4H, Ar-H), 7.28–7.32 m (1H, Ar-H), 7.40–7.46 m (2H, Ar-H), 7.59–7.62 d.d (*J* = 7.52 Hz, 1.75 Hz, 1H, Ar-H), 7.64–7.68 d (*J* = 16.06 Hz, 1H), 7.78–7.82 d (*J* = 16.06 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 21.3, 21.4, 25.9, 26.7, 64.5, 68.9, 115.0, 115.7, 121.5, 122.0, 122.9, 127.8, 128.7, 129.3, 130.8, 131.8, 133.7, 139.8, 157.8, 159.3, 191.0. Found, %: C 78.20; H 6.91. $C_{21}H_{22}O_3$. Calculated, %: C 78.23; H 6.88. *M* 323.

12-Chloro-7,8-dihydrodibenzo[*f,k*][1,5]dioxacyclododecin-14(6*H*)-one (5e). Yield 84%. Light yellow solid; mp 200–202°C. IR spectrum, ν, cm^{-1}: 1630, 1610, 1449, 1296, 1284. ^1H NMR spectrum, δ, ppm: 2.23–2.29 m (2H), 4.13–4.16 t (*J* = 5.27 Hz, 2H), 4.36–4.38 t (*J* = 5.52 Hz, 2H), 7.07–7.14 m (3H, Ar-H), 7.29–7.37 m (2H, Ar-H), 7.42–7.45 d.d (*J* = 8.78 Hz, 2.76 Hz, 1H, Ar-H), 7.49–7.53 d (*J* = 16.31 Hz, 1H), 7.56–7.60 d (*J* = 16.3 Hz, 1H), 7.682–7.689 d (*J* = 2.76 Hz, 1H, Ar-H). ^{13}C NMR spectrum, δ_C, ppm: 29.3, 67.1, 69.3, 117.5, 120.3, 123.9, 127.6, 128.6, 130.3, 130.6, 131.6, 131.7, 131.9, 132.8, 139.0, 156.6, 158.1, 191.4. Found, %: C 68.73; H 4.75. $C_{18}H_{15}ClO_3$. Calculated, %: C 68.68; H 4.80. *M 315*.

13-Chloro-8,9-dihydro-6*H*-dibenzo[*g,l*][1,6]-dioxacyclotridecin-15(7*H*)-one (5f). Yield 78%. Light yellow solid; mp 186–188°C. IR spectrum, ν, cm^{-1}: 1623, 1612, 1453, 1291, 1278. ^1H NMR spectrum, δ, ppm: 2.14–2.20 m (4H), 4.10–4.14 m (4H), 6.85–6.89 m (2H, Ar-H), 6.96–7.00 m (1H, Ar-H), 7.28–7.32 m (1H, Ar-H), 7.39–7.43 m (2H, Ar-H), 7.62–7.66 d (*J* = 15.8 Hz, 1H), 8.03–8.05 m (1H, Ar-H), 8.90–8.94 d (*J* = 15.8 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 25.9, 26.8, 68.3, 69.5, 111.6, 113.7, 120.7, 124.2, 126.0, 128.6, 130.6, 130.9, 131.5, 133.4, 134.5, 139.6, 157.9, 159.0, 189.0. Found, %: C 69.45; H 5.17. $C_{19}H_{17}ClO_3$. Calculated, %: C 69.41; H 5.21. *M* 329.

14-Chloro-7,8,9,10-tetrahydrodibenzo[*h,m*][1,7]-dioxacyclotetradecin-16(6*H*)-one (5g). Yield 75%. Light yellow solid; mp 132–134°C. IR spectrum, ν, cm^{-1}: 1629, 1611, 1457, 1293, 1281. ^1H NMR spectrum, δ, ppm: 1.89–1.97 m (6H), 4.13–4.16 m (2H), 4.18–4.21 m (2H), 6.88–6.90 d (*J* = 8.28 Hz, 1H, Ar-H), 6.93–6.99 m (2H, Ar-H), 7.29–7.33 m (1H, Ar-H), 7.36–7.39 d.d (*J* = 8.78 Hz, 2.76 Hz, 1H, Ar-H), 7.40–7.42 d.d (*J* = 7.52 Hz, 1.50 Hz, 1H, Ar-H), 7.651–7.652 d (*J* = 2.76 Hz, 1H, Ar-H), 7.68–7.72 d (*J* = 15.8 Hz, 1H), 8.13–8.17 d (*J* = 15.81 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 21.0, 25.9, 26.5, 65.1, 68.2, 112.2, 113.1, 120.8, 123.9, 125.8, 129.0, 130.7, 131.1, 131.2,

132.3, 135.0, 140.5, 156.1, 159.4, 191.9. Found, %: C 70.03; H 5.63. $C_{20}H_{19}ClO_3$. Calculated, %:: C 70.07; H 5.59. *M* 343.

15-Chloro-8,9,10,11-tetrahydro-6*H*-dibenzo[*i,n*]-[1,8]dioxacyclopentadecin-17(7*H*)-one (5h). Yield 69%. Light yellow solid; mp 138–140°C. IR spectrum, ν, cm^{-1}: 1624, 1613, 1458, 1299, 1281. ^1H NMR spectrum, δ, ppm: 1.63–1.72 m (4H), 1.82–1.88 m (4H), 4.16–4.18 t (*J* = 5.27 Hz, 2H), 4.28–4.31 t (*J* = 5.27 Hz, 2H), 6.89–6.92 d (*J* = 9.03 Hz, 1H, Ar-H), 6.95–7.02 m (2H, Ar-H), 7.32–7.40 m (2H, Ar-H), 7.46–7.48 d.d (*J* = 7.52 Hz, 1.75 Hz, 1H, Ar-H), 7.58–7.59 d (*J* = 2.76 Hz, 1H, Ar-H), 7.67–7.71 d (*J* = 15.8 Hz, 1H), 7.75–7.79 d (*J* = 16.06 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 21.1, 21.3, 26.0, 26.7, 68.5, 69.4, 115.0, 116.4, 122.0, 122.9, 127.5, 128.2, 128.7, 129.3, 129.6, 130.8, 133.1, 139.8, 156.5, 157.8, 190.5. Found, %: C 70.73; H 5.88. $C_{21}H_{21}ClO_3$. Calculated, %: C 70.68; H 5.93. *M* 357.

12-Fluoro-7,8-dihydrodibenzo[*f,k*][1,5]dioxacyclododecin-14(6*H*)-one (5i). Yield 83%. Light yellow solid; mp 210–212°C. IR spectrum, ν, cm^{-1}: 1620, 1611, 1455, 1295, 1283. ^1H NMR spectrum, δ, ppm: 2.23–2.29 m (2H), 4.13–4.16 m (2H), 4.35–4.38 t (*J* = 5.52 Hz, 2H), 7.08–7.21 m (4H, Ar-H), 7.29–7.34 m (1H, Ar-H), 7.35–7.38 m (1H, Ar-H), 7.41–7.44 d.d (*J* = 8.53 Hz, 3.26 Hz, 1H, Ar-H), 7.50–7.54 d (*J* = 16.06 Hz, 1H), 7.66–7.70 d (*J* = 16.06 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 29.4, 67.5, 69.2, 116.6, 116.8, 118.2, 118.3, 119.7, 119.9, 120.9, 124.0, 128.6, 130.6, 131.7, 132.0, 138.7, 154.3, 156.6, 158.2, 159.0, 191.3. Found, %: C 72.44; H 5.10. $C_{18}H_{15}FO_3$. Calculated, %: C 72.47; H 5.07. *M* 299.

13-Fluoro-8,9-dihydro-6*H*-dibenzo[*g,l*][1,6]-dioxacyclotridecin-15(7*H*)-one (5j). Yield 78%. Light yellow solid; mp 120–122°C. IR spectrum, ν, cm^{-1}: 1620, 1612, 1450, 1291, 1278. ^1H NMR spectrum, δ, ppm: 2.14–2.22 m (4H), 4.10–4.11 m (4H), 6.86–6.89 m (2H, Ar-H), 6.96–7.00 m (1H, Ar-H), 7.14–7.19 m (1H, Ar-H), 7.28–7.32 m (1H, Ar-H), 7.40–7.43 d.d (*J* = 7.52 Hz, 1.50 Hz, 1H, Ar-H), 7.63–7.67 d (*J* = 15.81 Hz, 1H), 7.77–7.80 d.d (*J* = 9.53 Hz, 3.26Hz, 1H, Ar-H), 8.95–8.99 d (*J* = 16.06 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 26.0, 26.7, 68.3, 69.6, 111.6, 113.4, 113.5, 117.7, 117.9, 120.2, 120.5, 120.7, 124.2, 128.4, 128.5, 130.6, 130.9, 134.5, 139.7, 155.6, 158.0, 159.0, 189.1. Found, %: C 73.01; H 5.54. $C_{19}H_{17}FO_3$. Calculated, %: C 73.06; H 5.49. *M* 313.

14-Fluoro-7,8,9,10-tetrahydrodibenzo[*h,m*][1,7]-dioxacyclotetradecin-16(6*H*)-one (5k). Yield 74%. Light yellow solid; mp 102–104°C. IR spectrum, ν, cm^{-1}: 1629, 1617, 1458, 1298, 1284. ^1H NMR spectrum, δ, ppm: 1.88–2.00 m (6H), 4.14–4.20 m (4H), 6.89–6.91 d (*J* = 8.82 Hz, 1H, Ar-H), 6.92–6.99 m (2H, Ar-H), 7.01–7.15 m (1H, Ar-H), 7.29–7.33 m (1H, Ar-H), 7.39–7.42 m (2H, Ar-H), 7.69–7.73 d (*J* = 16.06 Hz, 1H), 8.17–8.21 d (*J* = 15.81 Hz, 1H). ^{13}C NMR spectrum, δ_C, ppm: 21.2, 26.0, 26.5, 64.5, 68.3, 115.0, 115.1, 118.0, 118.1, 119.6, 119.8, 120.3, 120.4, 122.0, 122.9, 127.5, 128.7, 129.3, 130.8, 139.8, 154.2, 157.8, 159.4, 190.6. Found, %: C 73.54; H 5.93. $C_{20}H_{19}FO_3$. Calculated, %: C 73.60; H 5.87. *M* 327.

15-Fluoro-8,9,10,11-tetrahydro-6*H*-dibenzo[*i,n*]-[1,8]dioxacyclopentadecin-17(7*H*)-one (5l). Yield 66%. Light yellow solid; mp 96–98°C. IR spectrum, ν, cm^{-1}: 1622, 1613, 1453, 1288, 1276. ^1H NMR spectrum, δ, ppm: 1.61–1.87 m (8H), 3.96–4.16 m (4H), 6.69–6.72 m (1H, Ar-H), 6.76–6.81 m (2H, Ar-H), 6.85–6.93 m (1H, Ar-H), 6.95–7.08 m (1H, Ar-H), 7.10–7.13 m (1H, Ar-H), 7.20–7.26 m (1H, Ar-H), 7.32–7.36 m (1H), 7.66–7.69 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 21.3, 21.4, 26.1, 26.7, 68.1, 69.2, 109.4, 114.3, 114.4, 118.2, 118.9, 120.2, 120.6, 120.9, 121.9, 122.7, 123.3, 125.8, 128.5, 134.8, 142.8, 154.5, 158.4, 159.2, 191.2. Found, %: C 74.18; H 6.14. $C_{21}H_{21}FO_3$. Calculated, %: C 74.10; H 6.22. *M* 341.

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