DOI 10.1007/s10593-016-1939-y

Chemistry of Heterocyclic Compounds **2016**, *52*(8), 609–614

Synthesis and antimicrobial evaluation of novel pyrazole-annulated oxygen-containing macrocycles

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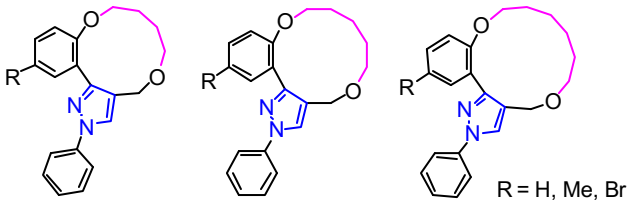
Published in Khimiya Geterotsiklicheskikh Soedinenii, 2016, *52*(8), 609–614

Submitted May 10, 2016
Accepted after revision July 13, 2016



An efficient approach to the synthesis of fused pyrazole-annulated macrocycles has been demonstrated. Vilsmeier–Haack reaction of substituted *o*-hydroxyacetophenones with phenyl hydrazine followed by reduction of the resulting pyrazolyl aldehydes yielded the corresponding alcohols. These precursors upon alkylation with dibromoalkanes gave the target library. The structures of the synthesized products were established based on ^{1}H, ^{13}C NMR, IR, and mass spectral data. All the final macrocycles were screened for their antimicrobial activity. Compounds bearing electron-donating groups show promising antimicrobial activity against the tested strains.

Keywords: macrocycles, pyrazole, Vilsmeier–Haack reagent, antimicrobial activity, dialkylation.

In recent years, macrocyclic compounds have found a variety of applications in the field of chemistry, biology, materials science, and nanotechnology.[1] Due to their conformational bias and flexible nature, these molecules are considered to be efficient molecular ligands for biological targets.[2] Particularly, small macrocyclic rings with heterocyclic motifs tend to be excellent molecular ligands because they are known to interact with distinct protein molecules. Hence, macrocyclic compounds have potential applications in drug development and discovery. In addition, some of them act as fluorescent sensors for chiral molecules and form complexes with small molecules in host–guest interactions.[3,4] There are many macrocyclic compounds known in the literature with potential biological activity.[5,6]

On the other hand, pyrazole and its derivatives represent a class of well-known nitrogen-containing heterocyclic compounds, which occupy an important position in medicinal and pesticide chemistry with a wide range of biological activity, such as antimicrobial,[7] anticancer,[8] anti-inflammatory,[9] antidepressant,[10] anticonvulsant,[10,11] anti-hyperglycemic,[12] antimetabolite,[13] and selective enzyme inhibitory effects.[14] Among the numerous known biologically active molecules of this class, pyraclostrobin and fipronil contain pyrazole framework (Fig. 1). Thus, in the light of the above findings and in the context of our[15] ongoing work regarding the synthesis of new heterocyclic compounds, we found it an attractive idea to construct new fused pyrazole-grafted macrocycles. Such compounds are not only synthetically challenging but may also be vitally important for pharmacological studies in the development of new medicinal properties. Therefore, we herein report the synthesis of a series of novel pyrazole-annulated oxygen-containing macrocycles (Fig. 1). The synthesized macrocycles were evaluated for their *in vitro* antimicrobial activity. Most of the compounds showed promising antimicrobial activity against the tested strains.

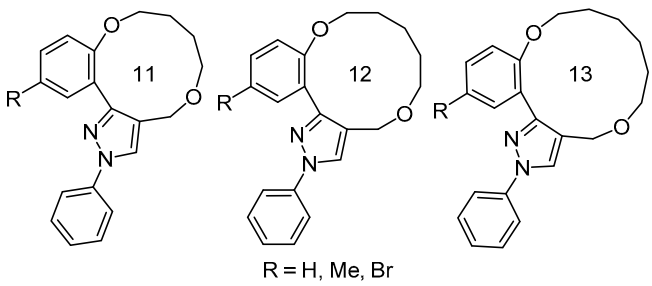
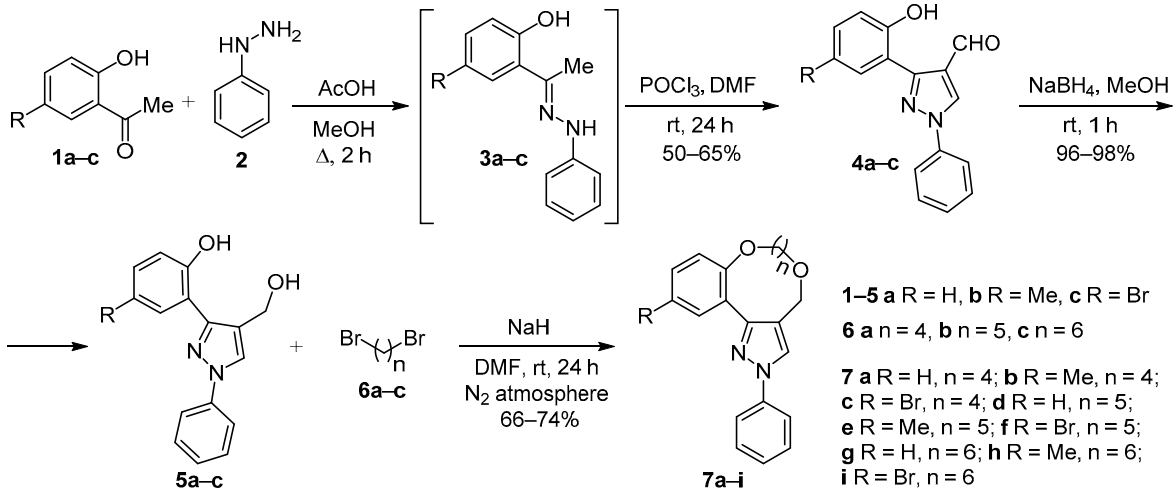


Figure 1. The proposed macrocycles containing a pyrazole scaffold.

Scheme 1



The synthetic route adopted for the preparation of fused pyrazole-grafted macrocycles is depicted in Scheme 1. The synthetic strategy begins with the condensation of substituted *o*-hydroxyacetophenones **1a**–**c** with phenylhydrazine (**2**) to efficiently provide the hydrazones **3a**–**c**. These derivatives **3a**–**c** were purified and transformed into the corresponding 3-(2-hydroxyaryl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **4a**–**c** by using the Vilsmeier–Haack reagent.[16] Pyrazole aldehydes were reduced to the corresponding alcohols **5a**–**c** by the action of $NaBH_4$ in methanol at room temperature. The structures of compounds **5a**–**c** were confirmed on the basis of spectroscopic data. The obtained substituted 2-[4-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]phenols **5a**–**c** were subjected to dialkylation with dibromoalkanes **6a**–**c** in the presence of sodium hydride for 24 h in DMF to afford the required fused macrocycles containing pyrazole framework **7a**–**i** in moderate to good yields.

All the synthesized macrocycles were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectral data. The ^{1}H NMR spectrum of compound **7a** (in $CDCl_3$) taken as an example, showed a singlet for the pyrazole ring proton at 7.99 ppm, and another singlet for the methylene protons at 4.38 ppm. Two triplets for two methylene groups adjacent to oxygen atoms appeared at 4.11 and 3.62 ppm, respectively. In addition, two *o*-methylene protons gave multiplets in the ranges of 1.86–1.90 and 1.78–1.82 ppm. The mass spectrum of compound **7a** revealed a peak at *m*/*z* 321 corresponding to its $[M+H]^+$ ion.

The newly synthesized compounds **7a**–**i** were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus* (ATCC 9144), *Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae (*ATCC 13048), and *Pseudomonas aeruginosa* (ATCC 19660) strains at 100 μg/ml concentration. Ampicillin was employed as the standard antibacterial drug. The results obtained as zone of inhibition in millimeters are presented in Table 1. Investigation of the antibacterial efficiency of the synthesized compounds revealed that most of the tested compounds displayed some inhibitory effects on the growth of the tested Gram-positive

Table 1. Antimicrobial activity of macrocycles **7a**–**i**, expressed as zone of inhibition in mm*

Compound	Bacterial strains				Fungal strains	
	S. aureus	*K. pneumoniae*	*E. coli*	*P. aeruginosa*	*A. flavus*	*F. oxysporum*
7a	4.0	4.5	6.0	5.0	<2.0	<2.0
7b	8.0	6.0	12.0	10.0	2.5	3.5
7c	6.0	4.5	8.5	7.5	<2.0	2.0
7d	5.5	3.0	9.5	8.5	4.0	3.5
7e	15.0	12.5	22.5	16.5	4.5	5.0
7f	10.5	8.0	15.0	11.5	<2.0	2.0
7g	8.0	4.5	8.0	11.0	<2.0	2.5
7h	18.0	15.5	27.0	21.0	5.5	6.0
7i	10.0	8.0	9.5	15.5	<2.0	<2.0
Ampicillin	20.0	17.0	33.0	25.0	–	–
Amphotericin B	–	–	–	–	16.4	18.6

* 10 μl of ampicillin (0.1 mg/ml) was used as a positive control. DMSO (10 μl of 0.8% aqueous solution) was used as negative control.

and Gram-negative bacterial strains. It is evident from Table 1 that compounds **7e**,**h** having an electron-donating group (methyl) at the fused benzene ring demonstrated a good zone of inhibition against all the bacterial strains compared to the standard. The remaining compounds were characterized by a smaller zone of inhibition against all the bacterial strains.

We have also tested the antifungal activity of these new macrocyclic compounds against two fungal strains, *Fusarium oxysporum* and *Aspergillus flavus*. The results of the antifungal screening were compared to the standard antifungal drug amphotericin B. All the macrocyclic compounds **7a**–**i** demonstrated low inhibitory activity against the tested fungal strains at 200 μg/ml concentration.

Thus, we have developed an efficient protocol for the synthesis of fused pyrazole macrocycles containing two oxygen atoms with moderate to good yields. These macrocycles are relatively accessible for further studies because they can be obtained through a facile, three-step synthesis with commercially available and relatively inexpensive chemicals. These pyrazole-fused macrocycles have been evaluated for their antimicrobial activity. Among the synthesized compounds, 14-methyl-2-phenyl-2,4,7,8,9,10-hexahydro-2*H*-benzo[5,6][1,7]dioxacyclododecino[4,3-*c*]-pyrazole and 15-methyl-2-phenyl-2,4,6,7,8,9,10,11-octahydro-benzo[5,6][1,7]dioxacyclotridecino[4,3-*c*]pyrazole having an electron-donating methyl substituent in the phenyl ring demonstrated good zone of inhibition against all the bacterial strains compared to ampicillin. The rest of the compounds showed moderate antimicrobial activity against all tested organisms. The experimental results of this study will likely provide a new basis for the design of interesting macrocycles during further studies, including the design of new analogs of these macrocycles with various biological activities.

Experimental

IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP1000 spectrometer. Elemental analyses were performed on a Carlo Erba EA1106 elemental analyzer. Melting points were determined in open capillary tubes on a Stuart SMP3 melting point apparatus and are uncorrected. Analytical TLC was performed on precoated Merck 60 F254 silica gel plates, visualization by exposing to iodine vapor and under UV light. All the reagents and solvents were purchased from commercial sources.

Synthesis of formylpyrazoles 4a–c as per modified literature procedure.[16] Step 1. Phenylhydrazine (**2**) (2.7 g, 1.7 ml, 24 mmol) was added to a solution of the appropriate 2-hydroxyacetophenone **1a**–**c** (24 mmol) in methanol (20 ml). The mixture was refluxed for 2 h in the presence of acetic acid (1.5 ml). After cooling of the reaction mixture, the phenylhydrazone intermediate crystallized and was filtered off.

Step 2. The appropriate 2-hydroxyacetophenone phenylhydrazone **3a**–**c** (0.01 mol) was dissolved in DMF (15 ml) and then $POCl_3$ (0.03 mol) was added dropwise at 0–5°C. After the addition of $POCl_3$ was finished, the reaction mixture was stirred at room temperature for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured onto crushed ice and then neutralized with 10% aqueous NaOH solution. The precipitate was filtered off, thoroughly washed with water, and recrystallized from ethanol.

3-(2-Hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4a). Yield 0.90 g (65%), light-yellow solid, mp 98–100°C. IR spectrum, ν, cm^{-1}: 3125 (OH), 2866, 1690 (CHO), 1529, 1500, 1249, 1210. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.01–7.05 (1H, m, H Ar); 7.12 (1H, d, *J* = 1.0, H Ar); 7.35–7.39 (1H, m, H Ar); 7.42–7.46 (1H, m, H Ar); 7.53–7.57 (2H, m, H Ar); 7.72–7.74 (2H, m, H Ar); 7.93–7.95 (1H, m, H Ar); 8.59 (1H, s, H pyrazole); 10.08 (1H, s, CHO); 10.20 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 114.8; 117.8; 119.1; 119.9; 124.1; 126.8; 129.5; 130.1; 130.3; 132.3; 139.8; 150.6; 155.1; 183.3 (CHO). Mass spectrum, *m*/*z*: 265 $[M+H]^+$. Found, %: C 72.68; H 4.56; N 10.54. $C_{16}H_{12}N_2O_2$. Calculated, %: C 72.72; H 4.58; N 10.60.

3-(2-Hydroxy-5-methylphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4b). Yield 0.69 g (50%), yellow solid, mp 58–60°C. IR spectrum, ν, cm^{-1}: 3120 (OH), 2856, 1686 (CHO), 1514, 1235, 1201. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3); 7.02 (1H, d, *J* = 8.3, H Ar); 7.17–7.19 (1H, m, H Ar); 7.35–7.36 (1H, m, H Ar); 7.41–7.45 (1H, m, H Ar); 7.52–7.56 (1H, m, H Ar); 7.72–7.74 (2H, m, H Ar); 7.83–7.84 (1H, m, H Ar); 8.59 (1H, s, H pyrazole); 9.78 (1H, s, OH); 10.11 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 21.7 (CH_3); 113.0; 117.4; 119.8; 120.5; 121.5; 128.5; 129.3; 131.4; 131.9; 132.8; 139.7; 151.6; 155.2; 184.5 (CHO). Mass spectrum, *m*/*z*: 279 $[M+H]^+$. Found, %: C 73.30; H 4.99; N 10.00. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.37; H 5.07; N 10.07.

3-(5-Bromo-2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4c). Yield 0.74 g (55%), yellow solid, mp 120–122°C. IR spectrum, ν, cm^{-1}: 3133 (OH), 2878, 1696 (CHO), 1535, 1506, 1254, 1218. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.00 (1H, d, *J* = 8.8, H Ar); 7.43–7.48 (2H, m, H Ar); 7.54–7.58 (2H, m, H Ar); 7.71–7.73 (2H, m, H Ar); 8.23 (1H, d, *J* = 2.3, H Ar); 8.59 (1H, s, H pyrazole); 10.18 (1H, s, CHO); 10.20 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 111.6; 117.1; 119.2; 119.7; 123.1; 128.7; 130.0; 132.0; 133.4; 133.8; 138.0; 151.2; 155.2; 183.6 (CHO). Mass spectrum, *m*/*z*: 343 $[M+H]^+$. Found, %: C 55.83; H 3.11; N 8.13. $C_{16}H_{11}BrN_2O_2$. Calculated, %: C 56.00; H 3.23; N 8.16.

Conversion of 4-formylpyrazoles 4a–c into respective pyrazole-2-phenols 5a–c (General method). Sodium borohydride (0.017 g, 0.94 mmol) was added slowly with stirring to a solution of 4-formylpyrazole **4a**–**c** (0.94 mmol) in MeOH (5 ml) at 0°C. The reaction mixture was stirred for 1 h at room temperature. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was poured into the ice-cold water. After 15 min, it was extracted with dichloromethane (3×10 ml) and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the corresponding alcohol **5a**–**c**.

2-[4-(Hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]phenol (5a). Yield 0.49 g (98%), yellow solid, mp 108–110°C. IR spectrum, ν, cm^{-1}: 3433 (OH), 3327 (CH_2–OH), 2924, 2853, 1597, 1503, 1391, 1359. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.87 (2H, s, C$\underline{H_2}$OH); 6.95–6.99 (1H, m, H Ar); 7.08 (1H, dd, *J* = 1.0, *J* = 7.3, H Ar); 7.27–7.34 (2H, m, H Ar); 7.45–7.49 (2H, m, H Ar); 7.64–7.66 (2H, m, H Ar); 7.74 (1H, dd, *J* = 1.5, *J* = 6.3, H Ar); 8.02 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 55.2 (CH_2OH); 117.2; 117.9; 119.3; 119.5; 120.5; 121.1; 124.2; 126.5; 129.5; 132.1; 140.1; 149.2; 155.1. Mass spectrum, *m*/*z* (I_{rel}, %): 267 $[M+H]^+$ (100). Found, %: C 72.11; H 5.25; N 10.48. $C_{16}H_{14}N_2O_2$. Calculated, %: C 72.17; H 5.30; N 10.52.

2-[4-(Hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]-4-methylphenol (5b). Yield 0.49 g (97%), light-yellow solid, mp 110–112°C. IR spectrum, ν, cm^{-1}: 3428 (OH), 3315 (CH_2–OH), 2918, 2849, 1588, 1389, 1249. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 4.86 (2H, s, C$\underline{H_2}$OH); 6.97 (1H, d, *J* = 8.3, H Ar); 7.06–7.08 (1H, m, H Ar); 7.29–7.33 (1H, m, H Ar); 7.44–7.48 (3H, m, H Ar); 7.61–7.63 (2H, m, H Ar); 7.75 (1H, dd, *J* = 1.5, *J* = 6.3, H Ar); 7.99 (1H, s, H pyrazole); 10.65 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 20.7 (CH_3); 56.5 (CH_2OH); 116.3; 116.8; 118.6; 121.1; 126.8; 127.7; 128.0; 128.5; 129.6; 130.3; 138.9; 149.8; 153.7. Mass spectrum, *m*/*z*: 281 $[M+H]^+$. Found, %: C 72.80; H 5.70; N 9.95. $C_{17}H_{16}N_2O_2$. Calculated, %: C 72.84; H 5.75; N 9.99.

4-Bromo-2-[4-(hydroxymethyl)-1-phenyl-1*H*-pyrazol-3-yl]phenol (5c). Yield 0.48 g (96%), yellow solid, mp 118–120°C. IR spectrum, ν, cm^{-1}: 3445 (OH), 3335 (CH_2–OH), 2933, 2868, 1601, 1515, 1397, 1364. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.87 (2H, d, *J* = 4.0, C$\underline{H_2}$OH); 6.97 (1H, d, *J* = 8.8, H Ar); 7.33–7.37 (2H, m, H Ar); 7.48–7.52 (2H, m, H Ar); 7.64–7.67 (2H, m, H Ar); 7.90 (1H, dd, *J* = 1.5, *J* = 7.8, H Ar); 8.06 (1H, s, H pyrazole); 10.91 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 56.2 (CH_2OH); 111.2; 118.4; 118.8; 119.1; 121.0; 127.2; 128.1; 129.7; 130.3; 132.2; 138.8; 148.8; 155.2. Mass spectrum, *m*/*z*: 344 $[M+H]^+$. Found, %: C 55.62; H 3.76; N 8.07. $C_{16}H_{13}BrN_2O_2$. Calculated, %: C 55.67; H 3.80; N 8.12.

Synthesis of macrocycles 7a–i (General method). Catalytic amount of sodium hydride (60% suspension in mineral oil, 20 mg, 1.1 mmol) was added to a well stirred solution of compound **5a–c** (0.375 mmol) in DMF (5 ml) under nitrogen atmosphere upon cooling. Dibromoalkane **6a–c** (0.375 mmol) was added, and the reaction mixture was stirred under room temperature for 24 h. The reaction progress was monitored by TLC (hexane–EtOAc, 7:3). After completion of the reaction, the mixture was poured into the ice-cold water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by column chromatography using hexane–ethyl acetate, 8:2, as an eluent to afford compound **7a–i**.

2-Phenyl-2,4,6,7,8,9-hexahydro[1,6]benzodioxacycloundecino[9,8-*c*]pyrazole (7a). Yield 0.20 g (70%), light-yellow solid, mp 85–87°C. IR spectrum, ν, cm^{-1}: 3345, 2939, 2876, 1616, 1535, 1376, 1356, 1012, 892, 699. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.78–1.82 (2H, m, CH_2); 1.86–1.90 (2H, m, CH_2); 3.62 (2H, t, *J* = 5.5, OCH_2); 4.09–4.12 (2H, t, *J* = 4.5, OCH_2); 4.38 (2H, s, $ArCH_2O$); 6.93 (1H, d, *J* = 8.3, H Ar); 6.99–7.02 (1H, m, H Ar); 7.27–7.28 (1H, m, H Ar); 7.34–7.38 (1H, m, H Ar); 7.41–7.45 (2H, m, H Ar); 7.52 (1H, dd, *J* = 1.5, *J* = 6.0, H Ar); 7.75–7.75 (2H, m, H Ar); 7.99 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 25.6; 27.6; 61.5; 67.8; 68.6; 111.0; 118.8; 119.4; 120.1; 122.3; 126.1; 128.0; 129.3; 129.8; 131.4; 140.0; 151.2; 157.1. Mass spectrum, *m*/*z*: 321 $[M+H]^+$. Found, %: C 74.94; H 6.25; N 8.70. $C_{20}H_{20}N_2O_2$. Calculated, %: C 74.98; H 6.29; N 8.74.

13-Methyl-2-phenyl-2,4,6,7,8,9-hexahydro[1,6]benzodioxacycloundecino[9,8-*c*]pyrazole (7b). Yield 0.25 g (72%), light-yellow solid, mp 88–90°C. IR spectrum, ν, cm^{-1}: 2923, 2866, 1665, 1545, 1396, 1377, 1238, 755, 689. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81–1.86 (2H, m, CH_2); 1.90–1.94 (2H, m, CH_2); 2.34 (3H, s, CH_3); 3.65 (2H, t, *J* = 5.0, OCH_2); 4.14 (2H, t, *J* = 4.5, OCH_2); 4.42 (2H, s, $ArCH_2O$); 6.94 (1H, d, *J* = 8.3, H Ar); 7.03–7.05 (1H, m, H Ar); 7.28–7.30 (1H, m, H Ar); 7.39–7.44 (1H, m, H Ar); 7.48–7.50 (1H, m, H Ar); 7.54 (1H, dd, *J* = 1.5, *J* = 6.0, H Ar); 7.75–7.78 (2H, m, H Ar); 7.96 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 21.5; 24.8; 27.2; 60.8; 66.8; 67.9; 110.6; 118.5; 119.1; 120.6; 122.0; 125.8; 128.2; 129.3; 130.6; 131.4; 139.7; 150.1; 156.1. Mass spectrum, *m*/*z*: 335 $[M+H]^+$. Found, %: C 75.38; H 6.58; N 8.34. $C_{21}H_{22}N_2O_2$. Calculated, %: C 75.42; H 6.63; N 8.38.

13-Bromo-2-phenyl-2,4,6,7,8,9-hexahydro[1,6]benzodioxacycloundecino[9,8-*c*]pyrazole (7c). Yield 0.20 g (71%), yellow solid, mp 82–84°C. IR spectrum, ν, cm^{-1}: 3344, 2870, 1615, 1519, 1356, 1315, 1045, 765, 665. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.77–1.82 (2H, m, CH_2); 1.87–1.92 (2H, m, CH_2); 3.60 (2H, t, *J* = 5.1, OCH_2); 4.10 (2H, t, *J* = 4.5, OCH_2); 4.40 (2H, s, $ArCH_2O$); 6.92 (1H, d, *J* = 8.3, H Ar); 7.03–7.05 (1H, m, H Ar); 7.27–7.28 (1H, m, H Ar); 7.34–7.35 (1H, m, H Ar); 7.43–7.45 (1H, m, H Ar); 7.51 (1H, dd, *J* = 1.5, *J* = 6.0, H Ar); 7.74–7.78 (2H, m, H Ar); 8.00 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 25.8; 27.6; 61.7; 66.8; 68.8; 111.5; 118.8; 119.5; 120.4; 121.8; 124.8; 127.5; 129.4; 131.4; 132.5; 140.2; 151.6; 156.1. Mass spectrum, *m*/*z*: 399 $[M+H]^+$. Found, %: C 60.10; H 4.75; N 6.97. $C_{20}H_{19}BrN_2O_2$. Calculated, %: C 60.16; H 4.80; N 7.02.

2-Phenyl-2,4,7,8,9,10-hexahydro-6*H*-[1,7]benzodioxacyclododecino[10,9-*c*]pyrazole (7d). Yield 0.19 g (68%), light-yellow solid, mp 100–102°C. IR spectrum, ν, cm^{-1}: 2919, 1600, 1503, 1459, 1242, 1066, 958, 751, 689. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60–1.65 (2H, m, $CH_2C\underline{H_2}CH_2$); 1.70–1.76 (2H, m, $CH_2CH_2C\underline{H_2}$); 1.81–1.86 (2H, m, C$\underline{H_2}CH_2CH_2$); 3.66 (2H, t, *J* = 7.0, OCH_2); 4.05 (2H, t, *J* = 4.5, OCH_2); 4.40 (2H, s, $ArCH_2O$); 6.95–7.04 (2H, m, H Ar); 7.28–7.29 (2H, m, H Ar); 7.40–7.46 (3H, m, H Ar); 7.75–7.77 (2H, m, H Ar); 8.09 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 17.0; 28.0; 28.4; 66.1; 69.7; 70.6; 116.4; 117.2; 119.0; 119.9; 120.8; 123.0; 126.2; 129.1; 129.3; 130.7; 139.7; 149.9; 154.1. Mass spectrum, *m*/*z*: 335 $[M+H]^+$. Found, %: C 75.38; H 6.60; N 8.32. $C_{21}H_{22}N_2O_2$. Calculated, %: C 75.42; H 6.63; N 8.38.

14-Methyl-2-phenyl-2,4,7,8,9,10-hexahydro-6*H*-[1,7]-benzodioxacyclododecino[10,9-*c*]pyrazole (7e). Yield 0.17 g (66%), white solid, mp 94–97°C. IR spectrum, ν, cm^{-1}: 2944, 1611, 1515, 1465, 1254, 1069, 945, 739, 669. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.59–1.62 (2H, m, $CH_2C\underline{H}_2CH_2$); 1.67–1.74 (2H, m, $CH_2CH_2C\underline{H}_2$); 1.80–1.85 (2H, m, $C\underline{H}_2CH_2CH_2$); 2.31 (3H, s, CH_3); 3.64 (2H, t, *J* = 7.0, OCH_2); 4.03 (2H, t, *J* = 4.5, OCH_2); 4.35 (2H, s, $ArCH_2O$); 6.92–6.94 (1H, m, H Ar); 6.96–7.00 (2H, m, H Ar); 7.27–7.29 (1H, m, H Ar); 7.33–7.36 (1H, m, H Ar); 7.39–7.44 (2H, m, H Ar); 7.72–7.74 (1H, m, H Ar); 8.00 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 15.2; 21.6; 28.4; 28.8; 66.0; 70.8; 71.6; 113.3; 117.2; 118.9; 119.0; 123.4; 126.2; 129.3; 129.6; 130.5; 131.1; 139.7; 150.1; 153.2. Mass spectrum, *m*/*z*: 349 $[M+H]^+$. Found, %: C 75.80; H 6.90; N 8.00. $C_{22}H_{24}N_2O_2$. Calculated, %: C 75.83; H 6.94; N 8.04.

14-Bromo-2-phenyl-2,4,7,8,9,10-hexahydro-6*H*-[1,7]-benzodioxacyclododecino[10,9-*c*]pyrazole (7f). Yield 0.20 g (70%), light-yellow solid, mp 98–100°C. IR spectrum, ν, cm^{-1}: 3015, 1632, 1520, 1489, 1233, 1071, 965, 746, 683. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60–1.65 (2H, m, $CH_2C\underline{H}_2CH_2$); 1.70–1.76 (2H, m, $CH_2CH_2C\underline{H}_2$); 1.81–1.86 (2H, m, $C\underline{H}_2CH_2CH_2$); 3.66 (2H, t, *J* = 7.0, OCH_2); 4.05 (2H, t, *J* = 4.5, OCH_2), 4.40 (2H, s, $ArCH_2O$); 6.96 (1H, d, *J* = 8.3, H Ar); 7.27–7.28 (2H, m, H Ar); 7.35–7.40 (1H, m, H Ar); 7.42–7.45 (2H, m, H Ar); 7.75–7.77 (2H, m, H Ar); 8.09 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 22.7; 28.4; 29.7; 59.8; 66.0; 68.8; 112.8; 117.2; 118.8; 119.9; 120.7; 124.2; 126.4; 129.4; 132.4; 134.6; 139.5; 149.5; 155.8. Mass spectrum, *m*/*z*: 413 $[M+H]^+$. Found, %: C 61.00; H 5.09; N 6.74. $C_{21}H_{21}BrN_2O_2$. Calculated, %: C 61.03; H 5.12; N 6.78.

2-Phenyl-2,4,6,7,8,9,10,11-octahydrobenzo[1,8]dioxacyclotridecino[11,10-*c*]pyrazole (7g). Yield 0.23 g (72%), white solid, mp 85–87°C. IR spectrum, ν, cm^{-1}: 3325, 2943, 2832, 1602, 1451, 1252, 1116, 1023, 758, 670. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37–1.40 (4H, m, $2CH_2$); 1.57–1.61 (2H, m, CH_2); 1.71–1.75 (2H, m, CH_2); 3.48 (2H, t, *J* = 5.5, OCH_2); 4.07 (2H, t, *J* = 5.5, OCH_2); 4.36 (2H, s, $ArCH_2O$); 6.98–7.02 (2H, m, H Ar); 7.28–7.31 (2H, m, H Ar); 7.35–7.40 (1H, m, H Ar); 7.43–7.47 (2H, m, H Ar); 7.79 (2H, d, *J* = 7.8, H Ar); 8.02 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 21.6; 22.3; 27.1; 27.7; 62.3; 65.7; 65.9; 112.1; 118.9; 119.0; 119.9; 122.2; 126.1; 127.5; 129.3; 129.8; 131.5; 140.0; 151.1; 157.8. Mass spectrum, *m*/*z*: 349 $[M+H]^+$. Found, %: C 75.75; H 6.90; N 8.00. $C_{22}H_{24}N_2O_2$. Calculated, %: C 75.83; H 6.94; N 8.04.

15-Methyl-2-phenyl-2,4,6,7,8,9,10,11-octahydrobenzo-[1,7]dioxacyclotridecino[11,10-*c*]pyrazole (7h). Yield 0.25 g (74%), white solid, mp 82–84°C. IR spectrum, ν, cm^{-1}: 3315, 2932, 2816, 1594, 1423, 1225, 1153, 1034, 735, 663. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35–1.39 (4H, m, $2CH_2$); 1.57–1.61 (2H, m, CH_2); 1.71–1.74 (2H, m, CH_2); 2.34 (3H, s, CH_3); 3.48 (2H, t, *J* = 5.5, OCH_2); 4.07 (2H, t, *J* = 5.5, OCH_2); 4.36 (2H, s, $ArCH_2O$); 7.00 (1H, t, *J* = 8.3, H Ar); 7.28–7.30 (1H, m, H Ar); 7.35–7.40 (1H, m, H Ar); 7.43–7.47 (3H, m, H Ar); 7.78 (2H, d, *J* = 7.8, H Ar); 8.02 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 21.8; 25.0; 25.5; 27.8; 28.0; 66.2; 69.7; 71.6; 113.3; 117.2; 118.9; 119.9; 123.4; 126.2; 129.3; 129.6; 130.5; 131.1; 139.7; 149.9; 151.1. Mass spectrum, *m*/*z*: 363 $[M+H]^+$. Found, %: C 76.15; H 7.20; N 7.70. $C_{23}H_{26}N_2O_2$. Calculated, %: C 76.21; H 7.23; N 7.73.

15-Bromo-2-phenyl-2,4,6,7,8,9,10,11-octahydrobenzo-[1,7]dioxacyclotridecino[11,10-*c*]pyrazole (7i). Yield 0.23 g (72%), brown solid, mp 92–95°C. IR spectrum, ν, cm^{-1}: 3338, 2961, 2845, 1615, 1462, 1242, 1121, 1032, 744, 695. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28–1.43 (4H, m, $2CH_2$); 1.56–1.65 (2H, m, CH_2); 1.68–1.72 (2H, m, CH_2); 3.45 (2H, t, *J* = 7.0, OCH_2); 4.02 (2H, t, *J* = 4.5, OCH_2); 4.33 (2H, s, $ArCH_2O$); 6.84 (1H, d, *J* = 8.7, H Ar); 7.27–7.28 (1H, m, H Ar); 7.40–7.46 (4H, m, H Ar); 7.75 (2H, d, *J* = 7.8, H Ar); 7.99 (1H, s, H pyrazole). ^{13}C NMR spectrum, δ, ppm: 21.6; 22.3; 27.0; 27.7; 29.7; 62.2; 66.1; 66.2; 112.0; 113.7; 119.0; 124.3; 126.3; 127.6; 129.3; 132.5; 134.1; 139.9; 149.7; 157.1. Mass spectrum, *m*/*z*: 427 $[M+H]^+$. Found, %: C 61.78; H 5.40; N 6.06. $C_{22}H_{23}BrN_2O_2$. Calculated, %: C 61.83; H 5.42; N 6.11.

Antimicrobial studies of the synthesized compounds 7a–i. *In vitro* antimicrobial studies were carried out by agar well diffusion method against test organisms.[17,18] Nutrient broth (NB) plates were swabbed with 24-h old broth culture (100 ml) of test bacteria. Using a sterile cork borer, wells (6 mm) were made in each Petri plate. Test samples in DMSO (100 μg/ml) were added into the wells by using sterile pipettes. Simultaneously, the standard antibiotics (ampicillin for antibacterial activity, amphotericin B for antifungal activity) were tested against the microorganisms. The plates were incubated at 37°C for 24 h. After appropriate incubation, the diameter of inhibition zone around each well was measured. Duplicates were maintained and the average values were calculated for finding the antibacterial as well as antifungal activity. The 24-h old cultures of the test bacteria *S. aureus* (ATCC 9144), *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 13048), and *P. aeruginosa* (ATCC 19660) were diluted 100-fold in nutrient broth (100 ml bacterial cultures in 10 l NB). All the tubes were incubated at 37°C for 24 h for bacteria and at 28°C for 48 h for fungi.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra is available at http://link.springer.com/journal/10593.

The authors are grateful to Department of Chemistry, Osmania University for providing laboratory facilities and the Central Facility for Research and Development, OU for providing spectral analysis. One of the authors, Mohan Gandhi Devulapally, is thankful to UGC-New Delhi for granting Senior Research Fellowship.

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