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ORIGINAL PAPER

Synthesis, characterization, and antioxidant activity of pyrazolic macrocycle

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Abstract A series of macrocycles containing isoxazoline, dioxazole, and pyrazole were synthesized and characterized by IR, ^{1}H, and ^{13}C NMR, mass spectra, elemental analysis, and X-ray single crystal determination. The antioxidant activity of synthesized compounds was evaluated. One of the compounds exhibits potent DPPH radical scavenging activity, comparable to that of vitamin E.

Keywords Cycloadditions · Macrocycles · Heterocycles · Antioxidant activity · DPPH

Introduction

Heterocyclic compounds, especially nitrogen heterocycles, are the most important class of compounds in the pharmaceutical and agrochemical industries, with heterocycles comprising around 60 % of all drug substances [1–3]. The pyrazole ring system, in particular, is a very common structural motif and is found in numerous biologically active natural products and pharmacologically relevant therapeutic agents [4–9]. Because of the significance of these scaffolds in drug discovery and medicinal chemistry, the development of new methodologies for the construction of novel heterocycles continues to be a very active field of research [10–12]. Following reports of these activities, this study seeks to an efficient synthetic method for macrocycles containing the pyrazole moiety with the aim of obtaining new biologically active compounds. In view of the continued interest in the development of simpler and more convenient synthetic routes for preparing macrocyclic systems, an efficient and useful method is reported herein to synthesize macrocycles using double different cycloadditions as cornerstones. In addition, pyrazole proved to be able to protect various tissues against oxidative stress, predominantly by scavenging deleterious reactive oxygen species. To the authors' knowledge, no investigation of the radical scavenging effects of synthesized pyrazolic macrocycle has yet been undertaken. It looked promising to support the development of new drugs and improve the treatment of various diseases.

Results and discussion

Synthetic methodology

The synthesis of pyrazolic macrocycle has been accomplished by cycloadditive macrocyclization route relies mainly bifunctional dipole (bis-nitrile oxides) and bifunctional dipolarophile in the presence of a base as triethylamine as outlined in Scheme 1. The bifunctional hydroxamic acid chloride **4** was prepared from the corresponding aldehyde **1** in a two-step procedure as given in Scheme 1. The structures of the cycloadducts were characterized by NMR spectroscopic data. The structures of all compounds are also confirmed by mass spectral analysis. The mass spectra show M^{+} peaks at corresponding masses of respective molecules.

The 1,3-dipolar cycloaddition of nitrile oxide and α,β-unsaturated ketones led to the formation of macrocycle **6** arising from the nitrile oxide addition to one C=C and C=O

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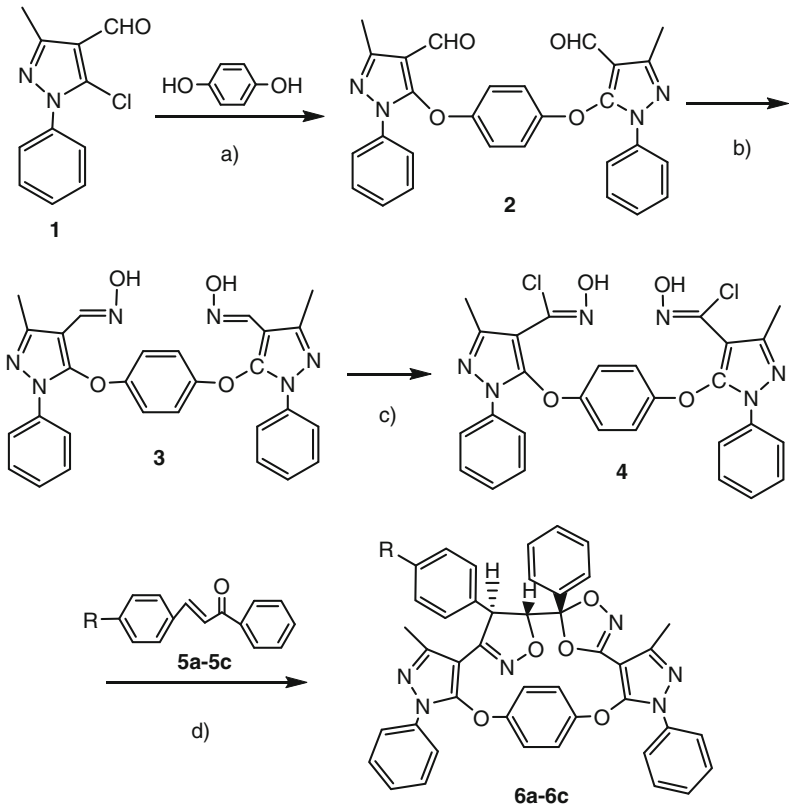
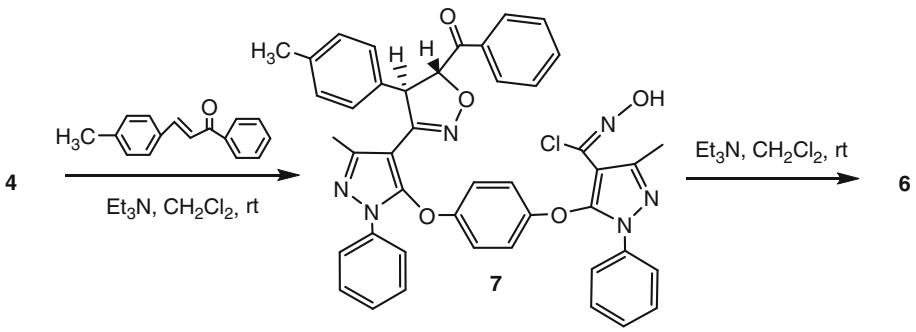
Scheme 1



R = H (**a**), OCH_3 (**b**), CH_3 (**c**)

Scheme 2



bonds. All of the cycloadducts **6a**–**6c** were separated through flash column chromatography using petroleum ether-ethyl acetate as eluent.

With a view to finding the order of occurrence of the cycloaddition of nitrile oxide to the C=C and C=O bonds leading to the formation of the cyclophane, the reaction was intercepted at early stages before completion of the reaction at 30 min and 1 h and the reaction mixture afford isoxazoline and failed to afford dioxazole (Scheme 2), thus suggesting that macrocycle **6c** might result from further cycloaddition to the intermediate **7**. To confirm this, the reaction of the intermediate with a nitrile oxide was performed in a separate experiment under the same reaction conditions as those of the overall reaction. This reaction furnished macrocycle **6c**, suggesting its formation from the intermediate **7**.

X-ray analysis

The structure of macrocycles was further confirmed by X-ray crystallographic studies of single crystals of **6c**. The structure of the crystal **6c** is displayed in Fig. 1, and a perspective view of the crystal packing in the unit cell is shown in Fig. 2.

X-ray diffraction study of the compound **6c** has shown that the title compound $C_{44}H_{34}N_6O_5$ crystallizes in the monoclinic system with space grouping C_2/c. The title molecule has a cyclic conformation, which consists of two pyrazole rings, an isoxazoline ring, and an oxadiazole ring. The O5, C42, O4, N6, and C44 atoms form a five-membered ring. X-ray analysis reveals that the five-membered

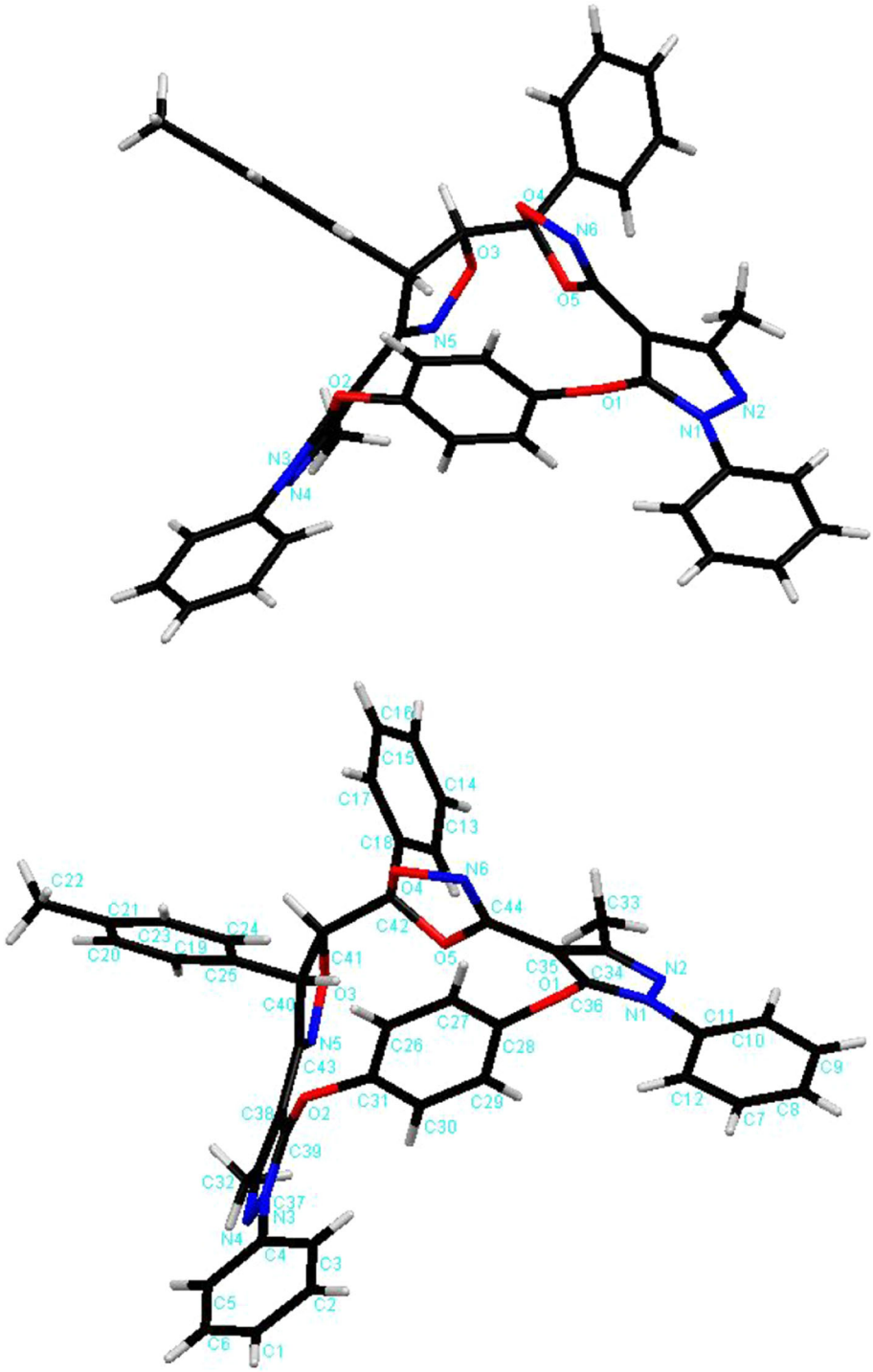


Fig. 1 X-ray crystal structure of macrocycle **6c**

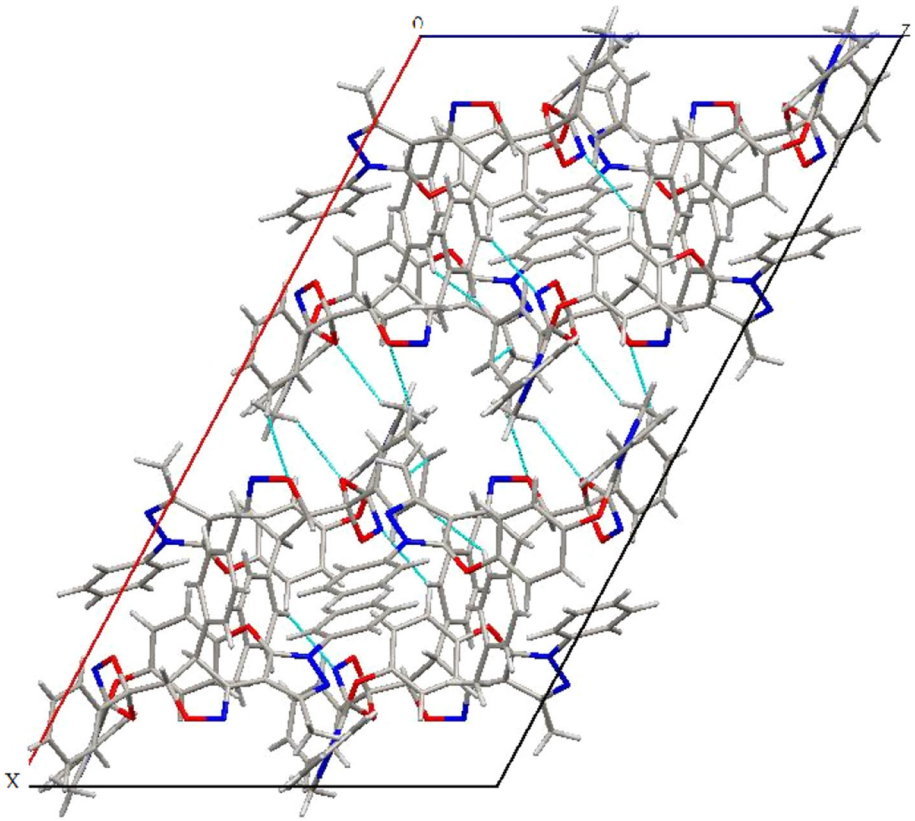


Fig. 2 Crystal packing diagram of **6c**

ring of dioxazole adopts an envelope conformation with the atom C42 deviating from the plane defined by the atoms O5, O4, N6, and C44 of 0.375 Å. Within the molecule, the C44–N6 (1.282 Å) and the C43–N5 (1.285 Å) bonds are shorter than the C36–N1 (1.347 Å) and C39–N3 (1.345 Å) bonds suggesting that the former two bonds have somewhat higher bond orders than the latter two bonds, because of the N6–C44 and C43–N5 bonds belong to double bond. The bond distances of C42–O5 (1.433 Å), C28–O1 (1.401 Å), and C41–O3 (1.456 Å) are significantly longer than a normal single C–O bond (1.367(3) Å). It is worth to illuminate that the C28–O1 (1.401 Å), C42–O5 (1.433 Å) bonds are longer than the C36–O1 (1.355 Å), C44–O5 (1.372 Å) bonds, largely due to intramolecular tension, but all lie within the range found in aromatic heterocycles [13]. The phenyl rings attached to N1 and N3 are twisted with respect to the pyrazole ring, the dihedral angles with the pyrazole ring being 27.3(3)° and 41.6(3)°, respectively. The phenyl groups of Cg(7) is nearly perpendicular to the oxadiazole ring attached to C42 with angle of 89.48(18)°. Similarly, the aryl ring attached to C40 is also twisted from the plane of the isoxazoline ring, the dihedral angle being 71.07(19)°. The plane of Cg(5) forms nearly equal dihedral angles with the other rings, 75.87(17)° with the pyrazole ring containing N2, N1 and 69.3(2)° with the pyrazole ring containing N3, N4. X-ray crystal structure determination indicates that there are eight independent molecules in the unit. In the crystal structure, there are no classic hydrogen bonds. QueryThe crystal structure is stabilized by weak C–H…N and C–H…O intramolecular hydrogen bonds and C…π stacking interactions, which are also observed between the neighboring molecules (Fig. 3; Table 1). Atoms C40, C24, and C6 act as a hydrogen-bond donor, respectively, via H…π bond to generate the super-molecular structures. The C atoms are involved in H…π interactions with the phenyl ring, which increase the stability of the 3D supramolecular architecture of the polymer. The perpendicular distance between ring centroids of Cg(2)–Cg(6), Cg(2)–Cg(7), Cg(8)–Cg(3), and Cg(5)–Cg(6) are 3.820(3) Å, 5.875(2) Å, 5.728(3) Å, and 5.729(2) Å, respectively. Furthermore, the bond lengths of C40-H…Cg(5), C36-H…Cg(2), and C49-H…Cg(6) correspond to 2.95, 2.71, and 2.96 Å, respectively [14]. $Cg(7)^{i}$ is the center of gravity of ring (C20, C31, C40, C41, C42, and C44) and $Cg(8)^{ii}$ is the center of gravity of ring (C34, C48, C52, C53, C58, and C45); symmetry code: i = $X,-Y,-1/2+Z$; ii = $-X,Y,1/2-Z$.

Evaluation of the antioxidant activity

The model of the scavenging of the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical is extensively used to

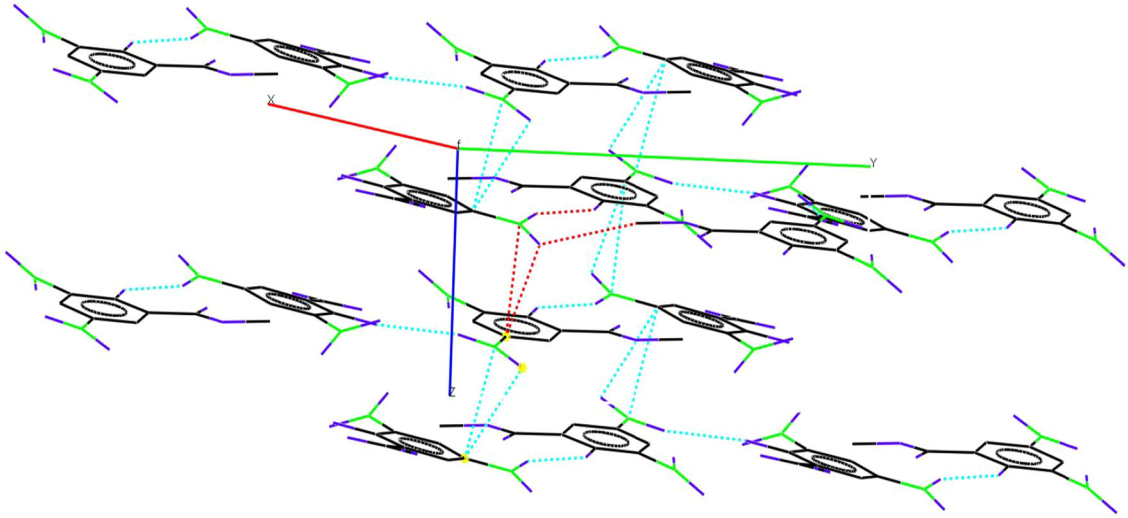


Fig. 3 The *blue* and *red dashed lines* indicates weak intermolecular interactions (color figure online)

Table 1 Intermolecular and intramolecular interactions in compounds

D–H…A	D–H	H…A	D…A	D–H…A
Intramolecular interactions				
C(9)–H(9A)…O(2)	0.98	2.50	2.874(4)	102
C(31)–H(31A)…O(1)	0.93	2.51	2.817(4)	100
C(52)–H(52A)…O(4)	0.93	2.44	2.944(6)	114
C(53)–H(53A)…N(1)	0.93	2.50	2.816(5)	100

D–H…A	H…A	D…A	D–H…A	Symmetry code
Intermolecular interactions				
C(9)–H(9A)–Cg(5)	2.95	3.841(3)	152	*X*,*Y*,*Z*
C(36)–H(36A)–Cg(2)	2.71	2.993(5)	99	*X*,*Y*,*Z*
C(49)–H(49A)–Cg(6)	2.96	3.780(7)	148	1/2-*X*,1/2-*Y*,-*Z*

Cg2 = O5–N6–C25–C9–C10; Cg5 = C11–C14–C12–C18–C13–C28; Cg6 = C19–C29–C37–C39–C32–C36

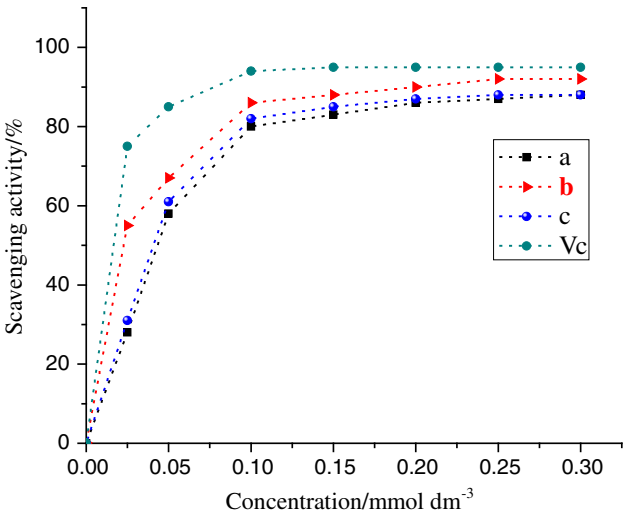


Fig. 4 Scavenging activity of compounds **6a–6c** on DPPH radical

evaluate antioxidant activities in less time than other methods. DPPH is a stable free radical that can accept an electron or hydrogen radical and thus be converted into a stable, diamagnetic molecule [15–17]. DPPH has an odd electron and so has a strong absorption band at 517 nm. When this electron becomes paired off, the absorption decreases stoichiometrically with respect to the number of electrons taken up. Such a change in the absorbance produced in this reaction has been widely applied to test the capacity of numerous molecules to act as free radical scavengers. The scavenging effect of the synthesized compounds **6a–6c** on the DPPH radical was evaluated [18–22]. All tests and analyses were undertaken on three replicates and the results averaged. The tests reveal that the more the concentration of the tested compound, the higher the radical scavenging activity. Compounds **6a–6c** exhibited good radical scavenging activity 80–85 % after standing 3 h at a final concentration of 0.1 mmol/dm^3. Compounds **6a**, **6c** exhibited 30–40 % radical scavenging activity in 30 min incubation at a final concentration of 0.1 mmol/dm^3. Compound **6b** with methoxy group scavenges DPPH radical very fast and the incubated time only takes 30 min to reach equilibrium. The profiles of the scavenging effect of compounds **6a–6c** on DPPH are comparable to that of vitamin E, and are presented in Fig. 4.

Conclusion

Various biologically active macrocycles that contain two pyrazole rings, an isoxazoline ring, and an oxadiazole moiety have been discovered or chemically synthesized. This work describes an efficient and convenient method for the synthesis of cyclophane. Macrocycles **6a–6c** were synthesized for the first time by the reaction of 1,3-dipolar cycloaddition of α,β-unsaturated ketones as key steps in the presence of triethylamine (Scheme 1). Among these, compounds **6a–6c** exhibit a potent DPPH radical scavenging activity, which is comparable to that of vitamin E.

Experimental

All purchased solvents and chemicals were of analytical grade and were used without further purification. Melting points were measured on a Mettler FP-5 capillary melting point apparatus. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The solid-state IR spectra were recorded from potassium bromide pellet on a Bruker Tensor 27 Spectrophotometer. The NMR spectra were recorded on a Varian Inova-400 spectrometer using $CDCl_3$ as the deuterated solvent and TMS as the internal standard at room temperature. EI-MS spectra were obtained with an Agilent 5975 apparatus. The results were found to be in good agreement with the calculated values. All reagents were of commercial availability. The compounds **1** [23], **2** [24], and **5** [25] can be synthesized as described according to the previously reported procedures.

5,5′-[1,4-Phenylenebis(oxy)]bis[3-methyl-1-phenyl-1H-pyrazole-4-carboxaldehyde] dioxime (**3**, $C_{28}H_{24}N_4O_4$)
To a solution of the dialdehyde **2** (4 mol) and $NH_2OH{\cdot}HCl$ (8 mol) in 60 cm^3 EtOH-H_2O was added an aqueous solution of NaOH (8 mol) dropwise. After stirring the suspension for overnight at 0 °C, the solid was collected by filtration and washed with water. The solid was crystallized from ethanol to give dialdoxime **3** as a pale-yellow solid. This compound was obtained as white crystals in 90 % yield. M.p.: 212–213 °C; IR (KBr): $\bar{\nu}$ = 3,429 (OH), 3,051 (Ar–H), 2,924, 1,474 (CH_3), 2,307 (C=N), 1,086 (C–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.59 (s, 2H, CH=N), 7.58-6.94 (m, 16H, Ar–H), 2.53 (s, 6H, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 152.5, 148.8, 137.9, 137.3, 131.5, 128.8, 126.4, 121.2, 119.1, 29.7, 14.0 ppm; MS(EI): *m/z* = 508 (M^+).

5,5′-[1,4-Phenylenebis(oxy)]bis[3-methyl-1-phenyl-1H-pyrazole-4-hydroxamic acid chloride]
(**4**, $C_{28}H_{22}N_4O_4Cl_2$)
To a solution of aldoxime **3** (10 mmol) in 12.5 cm^3 DMF was added *N*-chlorosuccinimide (15 mmol). The resulting mixture was stirred for 50 min. It was then poured into 80 cm^3 H_2O and extracted with EtOAc. The organic phase was washed several times with H_2O. The solid was collected by filtration and crystallized from ethanol to give bis(hydroxamic acid chloride) **4** as a white solid. This compound was obtained as white crystals in 88 % yield. M.p.: 180–181 °C; IR (KBr): $\bar{\nu}$ = 3,438 (OH), 3,051 (Ar–H), 2,974, 1,477 (CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–6.87 (m, 16H, Ar–H), 2.45 (s, 6H, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 152.3, 138.1, 137.6, 137.4, 131.7, 127.9, 126.4, 125.1, 117.5, 29.7, 14.0 ppm; MS (EI): *m/z* = 580 (M^+).

*General procedure for the preparation of macrocycles **6a–6c** by cycloadditive macrocyclization*

To a mixture of bis(hydroxamic acid chloride) **4** (2 mmol) and the chalcones **5** (2.5 mmol) in 50 cm^3 CH_2Cl_2 was added dropwise a solution of Et_3N (5 mmol) in 10 cm^3 CH_2Cl_2. Then, the solution was stirred at room temperature for further 12 h. The solid mass separated out was filtered off, and the solvent was evaporated in vacuo and the residue was subjected to flash column chromatography on silica gel (petroleum-ether:ethyl acetate 10:1) to afford macrocycles **6** as white crystalline solids.

5,15-Dimethyl-3,8,10,17-tetraphenylcalix[1]arene[2]-pyrazole[1]oxazole[1]isoxazole (**6a**, $C_{43}H_{32}N_6O_5$)
This compound was obtained as white crystals in 26 % yield. M.p.: 167–168 °C; IR (KBr): $\bar{\nu}$ = 3,051 (Ar–H), 1,567 (C=N), 2,924, 1,490 (CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–6.98 (m, 24H, Ar–H), 4.69–4.67 (d, 1H, H_5, J_{ab} = 8.40 Hz), 3.77–3.75 (d, 1H, H_4, J_{ab} = 8.40 Hz), 2.05 (s, 6H, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 157.4, 155.4, 152.3, 137.6, 135.0, 130.7, 129.6, 129.0, 128.9, 128.7, 126.8, 123.8, 121.3, 114.2, 109.6, 88.7, 57.5, 29.7, 12.9 ppm; MS (EI): *m/z* = 712 (M^+).

8-(4-Methoxyphenyl)-5,15-dimethyl-3,10,17-triphenylcalix[1]arene[2]pyrazole[1]oxazole[1]isoxazole
(**6b**, $C_{44}H_{34}N_6O_6$)
This compound was obtained as white crystals in 33 % yield. M.p.: 194–195 °C; IR (KBr): $\bar{\nu}$ = 3,045 (Ar–H), 1,581 (C=N), 2,924, 1,491 (CH_3) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–6.87 (m, 23H, Ar–H), 4.66–4.64 (d, 1H, H_5, J_{ab} = 8.40 Hz), 3.80 (s, 3H, –OCH_3), 3.72–3.70 (d, 1H, H_4, J_{ab} = 8.40 Hz), 2.05 (s, 6H, –CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 158.0, 157.3, 152.4, 150.0, 138.0, 135.0, 130.8, 127.4, 127.0, 124.7, 123.1, 122.8, 121.8, 121.0, 119.9, 115.5, 114.0, 109.2, 87.4, 56.6, 55.5, 29.7, 12.9 ppm; MS (EI): *m/z* = 742 (M^+).

5,15-Dimethyl-8-(4-methylphenyl)-3,10,17-triphenylcalix[1]arene[2]pyrazole[1]oxazole[1]-isoxazole (**6c**, $C_{44}H_{34}N_6O_5$)

This compound was obtained as white crystals in 32 % yield. M.p.: 182–183 °C; IR (KBr): $\bar{\nu}$ = 3,038 (Ar–H), 1,579 (C=N), 2,922, 1,487 (CH_3) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.71–6.95 (m, 23H, Ar–H), 4.65–4.63 (d, 1H, H_5, J_{ab} = 8.40 Hz), 3.83–3.81 (d, 1H, H_4, J_{ab} = 8.40 Hz), 2.49 (s, 3H, $–CH_3$), 2.05 (s, 6H, $–CH_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6, 157.4, 152.6, 151.6, 138.2, 135.9, 134.3, 134.2, 129.6, 129.0, 126.8, 125.9, 125.7, 121.7, 118.3, 115.4, 111.5, 109.2, 90.6, 59.7, 29.6, 21.5, 12.9 ppm; MS (EI): *m/z* = 726 (M^+).

Table 2 Crystal data and structure refinement for compound **6c**

Empirical formula	$C_{44}H_{34}N_6O_5$
Formula weight	726.77
Temperature/K	296(2)
Wavelength/Å	0.71073
Crystal system	Monoclinic
Space group	C2/*c*
a/Å	29.396(2)
b/Å	20.2506(15)
c/Å	16.5737(12)
α/°	90
β/°	118.345(2)
γ/°	90
V/Å^3	8,683.1(11)
Z	8
D_c/Mg m^{-3}	1.1119(1)
Crystal size/mm^3	0.57 × 0.41 × 0.7
θ range/°	1.57–27.52
μ/mm^{-1}	0.129
Reflections collected	38,747
Data/restraints/parameters	9,961/0/497
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.1097$, $wR2 = 0.3035$
R indices (all data)	$R1 = 0.1489$, $wR2 = 0.3515$

Crystal structure determination

The selected crystal with approximate dimensions of 0.57 × 0.41 × 0.7 mm^3 was mounted on thin glass fiber with the aid of an epoxy resin. The XRD data were collected with multi-scan mode at 296(2) K on a Bruker Smart AXSCCD with a graphite monochromatic Mo-Kα radiation (λ = 0.71073 Å). APEX2 software was used for data reduction and multi-scan absorption correction [26]. A total of 38,747 reflections ($2\theta_{max}$ = 55.04°) were collected, of which 9,961 unique reflections (R_{int} = 0.0349) were used for structural elucidation. The structures were solved by direct methods using SHELXS97 [27] and refinement was carried out by the full-matrix least-squares technique on F^2 using SHELXL97 [28]. The function $R\omega = |\sum\omega(|F_0|^2 - |F_c^2|/\sum^{|}\omega(f_0)^2|^{1/2}$ was minimized, where $\omega = [1/\sigma^2(F_0)^2 + (aP_0)^2 + bP]$ ($P = [F_0^2 + 2F_c^2]/3$). The final R_1 and wR_2 values 0.1097 and 0.3035 are for 5,960 independent reflections [$I > 2\sigma(I)$]. All non-hydrogen atoms were assigned anisotropic displacement parameters in the refinement. All hydrogen atoms were added at calculated positions and refined using a riding model, with C–H distances in the range 0.93 Å and with their U_{iso} set at 1.2 (1.4 for methyl groups) times the U_{eq} values of the appropriate carrier atoms. Molecular structure was checked using

Table 3 Selected bond lengths/Å, angles/°, and torsion angles/° of compound **6c**

O(1)–C(7)	1.433(3)	O(1)–C(8)	1.371(3)
O(2)–N(3)	1.439(3)	O(2)–C(7)	1.433(4)
N(3)–C(8)	1.282(4)	O(5)–N(6)	1.420(4)
O(5)–C(10)	1.456(4)	C(9)–C(10)	1.536(5)
C(9)–C(25)	1.504(4)	N(6)–C(25)	1.285(5)
C(7)–C(10)	1.538(5)	C(8)–C(16)	1.457(4)
C(25)–C(26)	1.467(5)	O(3)–C(14)	1.404(4)
O(3)–C(23)	1.352(4)	O(4)–C(13)	1.401(4)
O(4)–C(24)	1.354(5)	N(1)–N(2)	1.383(5)
N(4)–N(5)	1.369(4)	C(14)–O(3)–C(23)	115.8(3)
N(3)–O(2)–C(7)	106.0(2)	C(7)–O(1)–C(8)	103.5(2)
O(1)–C(8)–N(3)	115.6(3)	O(1)–C(7)–C(10)	111.1(2)
C(7)–C(10)–C(9)	117.1(2)	C(13)–O(4)–C(24)	113.7(3)
C(8)–C(16)–C(24)–O(4)	−1.7(5)	O(1)–C(7)–C(10)–O(5)	−52.7(3)
O(1)–C(7)–C(10)–C(9)	67.2(4)	O(2)–C(7)–C(10)–O(5)	−165.3(2)
O(2)–C(7)–C(10)–C(9)	−45.5(3)	O(3)–C(23)–C(26)–C(25)	2.1(7)
C(14)–O(3)–C(23)–C(26)	−65.2(5)	C(13)–O(4)–C(24)–C(16)	50.3(4)

PLATON [18]. All crystal data and structure refinements are listed in Table 2, selected length, angles, and torsion angles are tabulated in Table 3 and intramolecular and intermolecular interactions are shown in Table 1.

CCDC-832509 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via e-mail: data_request@ccdc.cam.ac.uk.

Evaluation of the antioxidant activity

The free radical scavenging effect of the synthesized compounds **6a–6c** on the stable DPPH radical was evaluated [15–17]. Various concentrations of the test compound were dissolved in 12.5 cm^3 of methanol in a volumetric flask, and then 12.5 cm^3 of a methanolic solution of DPPH (0.2 mmol/dm^3) were added to obtain a solution of DPPH (final concentration of DPPH was 0.1 mmol/dm^3). The mixture was shaken vigorously and incubated in a water bath at 25 °C for 30 min. The absorbance of the remaining DPPH was determined colorimetrically at 517 nm. The same reaction conditions were applied for the blank test compound to evaluate the interference of the title compound on DPPH assay. The scavenging activity of the tested title compound was measured as the decrease in absorbance of the DPPH, and the percentage of activity was calculated. Vitamin E was used as a reference compound. All tests and analyses were undertaken on three replicates and the results averaged. Calculated according to the formula

$$\text{Scavenging activity } (\%) = [[(A_b + A_s) - A_m]/A_b] \times 100\ \%$$

where A_b is the absorbance of 0.1 mmol/dm^3 DPPH methanol solution at 517 nm, A_s the absorbance of various concentration solution of test compound at 517 nm, A_m the absorbance of mixture methanol solution at 517 nm.

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