

Crowned Macrocycles Containing Two Pyrrolo[1,2-a] Indoles Created By Intramolecular Fusion

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Abstract: Heterocyclic fused-ring systems are of utmost importance because of their presence in many natural products with biological activity. Pyrroloindoles are tricyclic heterocycles that are present in various bioactive and medicinally valuable compounds. Herein, we report the synthesis of phenylene-bridged bis-pyrrolo[1,2-a]indole crowned macrocycles 1–3 in which the pyrrolo[1,2-a]indole moieties were formed *via* intramolecular fusion. The macrocycles were thoroughly characterized by 1D and 2D NMR, HRMS and X-ray crystallographic studies. The X-ray structure revealed that the two pyrrolo[1,2-a]indole moieties were parallel to each other, and one pyrrolo[1,2-a]indole unit was

Introduction

Heterocyclic fused-ring systems with ring junction nitrogen atom(s) are of interest because they constitute an important class of natural products, many of which exhibit useful biological activity.^[1-8] Pyrrolo[1.2-a]indole is one such class of heterocyclic fused ring systems with utmost importance in biology and medicine.^[9-14] These tricyclic indole derivatives are found in many natural products and pharmaceuticals and proved to be valuable intermediates for synthesizing more complex alkaloids. Pyrrolo[1.2-a]indole scaffolds present in numerous bioactive compounds such as mitomycin A and C, which acts as anti-tumor agents, antiparasitic isoborreverine, antimalarial alkaloid Flinderole C and Isatisine A which acts as anti-HIV agent to name a few.[11,15-18] Because of their significant importance as bioactive and medicinally important compounds, many synthetic pathways have been developed to synthesize pyrrolo[1,2-a]indoles and their derivatives. Pyrrolo[1,2-a]indole scaffold exists as three structural isomers, namely, 9H-pyrrolo [1,2-a]indole I, 1H-pyrrolo[1,2-a]indole II and 3H-pyrrolo[1,2-a] indole III, depending on conjugation and position of the sp3 carbon (Scheme 1).^[19] A perusal of literature reveals very few reports on macrocycles that contain pyrrolo[1,2-a]indole moiety as a part of the macrocyclic framework. Recently, we reported the synthesis of crowned 3H-pyrrolo[1,2-a]indole fluorophore macrocycles IV using readily available precursors under acidcatalyzed reaction conditions.^[20] In crowned fluorophore macrocycles, the pyrrolo[1,2-a]indole unit was created during the

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deviated by an angle of 9.54° while the other pyrrolo[1,2-a] indole unit was deviated by an angle of 12.0° from the mean plane defined by 28 core atoms. The macrocycles **1–3** absorb in the visible region and readily undergo oxidations because of their electron rich nature. The macrocycles **1–3** upon treatment with trifluoroacetic acid (TFA) generates the corresponding cation radicals **1–3°**⁺ which were stable in the open air for a week. The cation radicals **1–3°**⁺ absorb strongly in the NIR region and the experimental observations on crowned macrocycles **1–3** were corroborated by DFT and TD-DFT studies.

oxidation step of the reaction. In continuation of our work on pyrrolo[1,2-a]indole containing macrocycles, herein we report the synthesis of a new type of crowned macrocycles 1-3 that contain two pyrrolo[1,2-a] moieties as a part of the macrocyclic framework.

Results and Discussion

The phenylene bridged bis-pyrrolo[1,2-a]indole crowned macrocycles 1-3 were synthesized as shown in Scheme 2. The desired key precursors 5 and 6 were synthesized by adopting literature procedures.^[21,22] The *p*-hydroxy benzaldehyde was treated with bis (2-chloroethyl) ether at reflux for two days to afford 7. In the subsequent step, the compound 7 was subjected to Grignard reaction with two different ArMgBr to afford diols 5 a and 5 b in 45-48% yields. On the other hand, terephthalaldehyde was treated with two different ArMgBr under Grignard reaction conditions to afford diols 8, which were then treated with excess pyrrole under mild acid-catalyzed conditions to afford benzitripyrranes 6a and 6b in 60-65% yields. The phenylene bridged bis-pyrrolo[1,2-a]indole crowned macrocycles 1-3 were synthesized by condensing one equivalent of appropriate diol 5a/5b with one equivalent of benzitripyrrane 6a/6b in CH₂Cl₂ in the presence of a catalytic amount of BF₃.OEt₂ under inert atmosphere at room temperature for 10 min followed by oxidation with DDQ in the open air for an additional 30 min. TLC analysis showed one less polar major spot corresponding to the desired crowned macrocycle 1-3, and a more polar minor spot corresponding to our earlier reported macrocycle IV and one or two more polar unidentified minor spots. The formation of compound IV during the condensation was due to scrambling in presence acid catalyst which is a known phenomenon in porphyrinoid chemistry.^[23,24] Column chromatographic purification on basic alumina afforded crowned macro-



IV

Scheme 1. Structures of various pyrrolo[1,2-a]indole scaffolds and pyrrolo[1,2-a]indole based macrocycles.

cycles 1-3 as violet solids in 10-15% yields. The condensation of diol 5a/5b and benzitripyrrane 6a/6b were also carried out by using the other acid catalysts such as TFA and PTSA under different reaction conditions, but the best yields of crowned macrocycles 1-3 were obtained only with 0.1 equivalent of BF₃.OEt₂ as an acid catalyst. The macrocycles 1–3 are highly soluble in common organic solvents like CH₂Cl₂, CHCl₃, THF, and HR-MS analysis showed four mass units less than the expected macrocycle 4 indicating the occurrence of two intramolecular fusion reactions between pyrrolic "N" and benzene "C" to create two pyrrolo[1,2-a]indole units as a part of the macrocyclic skeleton to form macrocycles 1-3 as we noted previously with macrocycle IV.^[20] The formation of macrocycles 1-3 with two pyrrolo[1,2-a]indole moieties was later confirmed by obtaining crystal structure of macrocycle 2 (vide-infra). The compounds 1-3 were further characterized by detailed 1D and 2D NMR, and the ¹H NMR, ¹H-¹H COSY and NOESY and the selected region of macrocycle 2 are presented in Figure 1. We made an attempt to identify the resonances in ¹H NMR based on their location, integration, coupling constant, cross-peak connectivities observed in COSY and NOESY spectra. However, due to the overlap of resonances, we identified and assigned few resonances, as shown in Figure 1. Since the macrocycle was

highly distorted, we noted two resonances at 2.28 and 2.41 ppm for meso-tolyl –CH₃ protons; a bunch of resonances in the region of 3.6-4.4 ppm corresponding to -OCH₂ protons of crown ether moiety and a singlet resonance at 4.43 ppm for anisyl -OCH₃ protons. The four pyrrole protons of two pyrrolo [1,2-a]indole moieties have appeared as three resonances at 6.57, 6.77 and 6.22 ppm; the four outer protons of benzene rings (type d, g, e, h) of pyrrolo[1,2-a]indole moieties appeared at 6.54, 6.77, 7.51-7.64 ppm, whereas the two inner protons (type f and c) appeared as two doublets at 5.45 and 6.09 ppm. The four protons resonances of *p*-phenylene ring of the macrocycle overlapped with meso-aryl protons. The other two macrocycles 1 and 3 have also shown similar NMR features. Since the macrocycles 1-3 showed unsymmetric ¹H NMR spectra, we recorded the ¹H NMR of compound 2 in pyridine-d5 at higher temperatures (55°C and 85°C), but the spectra remained unsymmetric (Figure S10) suggesting a high remarkable conformational stability of compound 2. Thus, NMR studies helped to deduce the molecular structure of macrocycles 1-3.



Scheme 2. Synthesis of phenylene bridged bis-pyrrolo[1,2-a]indole crowned macrocycles 1–3.

Crystallographic Studies

The diffraction quality single crystals of macrocycle **2** were grown by slow diffusion of n-hexane into chloroform solution at room temperature over a period of 7 days. The macrocycle **2**

crystalized in a triclinic system with *P*-1 space group, and the important crystallographic parameters are given in supporting information (Table S1–S3). The crystal structure of compound **2** presented in Figure 2 revealed that macrocycle **2** contained two pyrrolo[1,2-a]indole moieties, one *p*-phenylene ring, two *meso*

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Figure 1. (a) Partial ¹H NMR (b) partial ¹H-¹H COSY and (c) partial ¹H-¹H NOESY spectra of compound 2 recorded in CDCl₃.



Figure 2. X-ray crystal structures of the compound 2 (a) top view; and (b) side view. The meso groups were omitted for the clarity of the side view.

carbon atoms and a long ether chain connected to each other in a cyclic fashion. The pyrrole ring C fused with the benzene ring A, creating a pyrrolo[1,2-a]indole unit A-B-C whereas the pyrrole ring F fused with the benzene ring D generating another pyrrolo[1,2-a]indole unit D-E-F. Thus, in compound 2, the two pyrrolo indole units (A-B-C and D-E-F) were connected by a long-distorted ether chain containing three oxygen atoms (O1, O2, O3), four carbon atoms (C25–C28) at one side and a benzene ring I with two *meso* carbon atoms (C6, C13) on the other side. The mean plane is defined by considering both the

Chem Asian J. 2021, 16, 1–10 www.chemasianj.org 4 These are not the final page numbers! pyrrolo[1,2-a]indole units, two *meso*-carbons and 1,4-carbon atoms of phenylene moiety consisting of 28 atoms in total. The pyrrolo[1,2-a]indole unit **A-B-C** (12 atoms) was deviated from the mean plane by an angle of 9.54°, whereas the pyrrolo[1,2-a] indole unit **D-E-F** (12 atoms) was deviated by an angle of 12.01°. However, the two pyrrolo[1,2-a]indole units were almost parallel to each other. The benzene ring I deviated from the

Table 1. Photophysical and Electrochemical Data of compounds 1–3.						
Compounds	Absorption $\lambda_{abs}[nm]$ [log ϵ]	data $\lambda_{abs}[nm]$ [log ϵ]	Electroc E _{1/2ox} [V]	hemical c E _{1/2ox} [V]	lata E _{1/2ox} [V]	E _{1/2Rdx} [V]
1	285 [4.87]	551 [4.71]	0.621	0.770	1.20	-1.27
2	285 [4.84]	551 [4.70]	0.557	0.688	1.16	-1.35
3	285 [4.80]	552 [4.67]	0.556	0.679	1.06	-1.31
IV	280 [4.85]	469 [4.27]	0.79	1.25	-	-1.61
1**	533 [5.00]	1144 [4.27]	-	-	-	-
2**	478 [4.74]	1109 [4.28]	-	-	-	-
3*+	529 [4.78]	1112 [4.17]	-	-	-	-
IV*+	381 [2.73]	628 [4.50]	-	-	-	-

mean plane by an angle of 66.9° . The two tolyl groups on the *meso* carbon atoms were anti-parallel to each other. The tolyl ring **H** at C6 *meso* carbon was oriented towards the macrocyclic core by making an angle of 55.3° with the mean plane. In contrast, the tolyl ring **G** at C13 *meso* carbon was away from the core of the macrocycle by making an angle of 59.3° . Overall, the X-ray crystallographic studies revealed non-planarity in the macrocyclic structure.

Absorption and electrochemical studies

The absorption and redox potentials of macrocycles 1–3 were measured, and the relevant data are tabulated in Table 1. The comparison of absorption spectra of macrocycles 1–3 along with macrocycle IV recorded in CHCl₃ is presented in Figure 3a. In general, the macrocycles 1–3 showed one sharp band at 300 nm and a broad band at ~550 nm with a shoulder at ~400 nm. The absorption spectra of compounds 1–3 were red shifted compared to that of the contracted macrocycle IV by ~100 nm, which was attributed to the extended π -conjugation in macrocycles 1–3. The macrocycles 1–3 were non-fluorescent, unlike fluorescent macrocycle IV in spite of the presence of two pyrrolo[1,2-a]indole moieties in macrocycles 1–3, which was tentatively attributed to higher vibrational relaxations in macro-



Figure 3. (a) Comparison of absorption spectra of the compounds 1–3 and IV (2×10^{-5} M) recorded in CHCl₃ at room temperature, (b) Comparison of cyclic voltammograms of the compounds 1 and IV recorded in CH₂Cl₂ using saturated calomel electrode as reference electrode and 0.1 M TBAP as supporting electrolyte. (c) Change in the absorption spectra and colour of the compounds 1 (2×10^{-5} M) upon systematic addition of TFA (1–8% v/v) recorded in CHCl₃ at room temperature (d) EPR spectra of 1–3⁺⁺ recorded in CHCl₃.

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cycles 1-3.^[25,26] To further understand the electronic properties of macrocycles 1-3, cyclic voltametric and differential pulse voltametric studies were performed on macrocycles 1-3 (Figure S11). The comparison of oxidation waves of macrocycles 1 and IV is shown in Figure 3b, and the data is included in Table 1. The cyclic voltametric studies revealed that the macrocycles 1-3 have three reversible oxidations and one quasireversible reduction whereas macrocycle IV showed two reversible oxidations and one irreversible reduction. For example, the macrocycle 1 showed three reversible oxidations at 0.62 V, 0.77 V, 1.2 V, and one quasi-reversible reduction at -1.27 V. In comparison to compound IV, compounds 1-3 have lower oxidation potentials and higher reduction potentials (Table 1), suggesting that compounds 1-3 were easier to oxidize and reduce compared to compound IV. Among macrocycles 1-3, macrocycles 2 and 3 were easier to oxidize compared to macrocycle 1 due to the presence of electrondonating meso-anisyl groups. Thus, macrocycles 1-3 were electron-rich and easier to oxidize.

Formation of cation radical

Since the macrocycles 1-3 are highly electron rich and our earlier study on similar kind of macrocycle IV, which is contracted compared to the compounds 1-3 showed that these types of compounds can easily form cation radicals, so we have oxidized these macrocycles 1-3 by treating them with TFA as well as $AgSbF_6$ and $CuCl_2$.^[20] The macrocycles 1-3 upon treatment with TFA readily formed cation radicals 1-3^{•+} as evident from clear colour change from violet to blue and confirmed by electron paramagnetic resonance and spectral absorption studies.^[27] The electron paramagnetic resonance spectrum of generated cation radicals 1-3°+ showed one sharp resonance with a g value of ~2.005 (Figure 3d). The formation of cation radical was also evident from spectral absorption studies. The absorption spectral changes upon systematic titration of macrocycle 1 with increasing amounts of TFA is presented in Figure 3c. Upon increasing the amounts of TFA to macrocycle 1, the absorption band at 550 nm was hypsochromically shifted to 533 nm with increasing intensity along with the appearance new broad band in the region of 850-1400 nm with a peak maxima of 1144 nm due to the formation of cation radical 1^{•+}. These observations were in line with our previous studies on macrocycle IV. However, the lower energy absorption band of 1-3^{•+} was 500 nm bathochromically shifted compared to cation radical IV^{•+,} which was observed at 628 nm. (Figure S12) Thus, the significant red shift in the absorption band of cation radical 1^{•+} compared to $IV^{\bullet+}$ was attributed to the enhanced π conjugation in macrocycle 1. The ¹H NMR spectrum of 1^{•+} is broadened, and very few resonances appeared supporting the paramagnetic nature of the compound (Figure S14). Furthermore, a stability study on the generated cation radical 1^{•+} was performed by recording the absorption and EPR spectra of the solution of 1^{•+} stored under an open atmosphere over a period of 1 week. The studies indicated that the cation radical was stable for up to one week at room temperature in open atmospheric conditions (Figure S15). Similar observation of formation of cation radicals were also noted when compound 1 was treted with $AgSbF_6$ and $CuCl_2$ (Figure S13).

DFT Studies

To further understand the electronic structure of macrocycle 1-3 and their cation radicals 1-3^{•+}, density functional theory $(\mathsf{DFT})^{\scriptscriptstyle[28]}$ and $\mathsf{TD}\text{-}\mathsf{DFT}^{\scriptscriptstyle[29-31]}$ calculations were carried out at uB3LYP/6-31G (d,p)^[32,33] level of theory, and the ground state optimized structures along with the structural parameters have been given in Figure S16 and Table S4-9. The ground state optimized structure of macrocycle 2 closely matched with the X-ray crystal structure of 2 where the aryl groups on two pyrrolo[1,2-a]indole moieties were oriented away from the macrocyclic core. However, one of the aryl group present at the meso carbon bridging the pyrrolo[1,2-a]indole moiety and phenylene moiety was oriented away from the core whereas the other meso-aryl group was oriented towards the macrocyclic core. The frontier molecular orbital (FMO) analysis of the macrocycle 1-3 showed that the HOMO and LUMO were present all over the macrocycle with a negligible contribution from crowned moiety with a HOMO-LUMO gap of 2.22 eV, 2.19 eV, 2.17 eV, respectively, for macrocycles 1, 2 and 3 (Figure S17). As we move from macrocycle 1 to 3, all the FMO orbitals were slightly destabilized. HOMO and LUMO of compound 3 were relatively destabilized compared to that of compound 2, which were further destabilized compared to that of compound 1. This upward trend of destabilization of HOMO and LUMO led to lower oxidation as well as reduction potential for compound 3 compared to compounds 1 and 2, which is in agreement with data obtained from electrochemical experiments (Figure S11). It was noted that as the number of anisyl groups at the meso position of the macrocycle was increased, the macrocycle became relatively easier to oxidize and reduce. TD-DFT studies showed that these macrocycles 1-3 absorb in visible region with peak absorption corresponds to HOMO-LUMO transition at ~660 nm which is in line with the observed absorption spectra of macrocycles 1-3 (Figure S18-20).

Since the macrocycles 1-3 are electronically rich and easily oxidized to their corresponding cation radicals 1-3°+, DFT, as well as TD-DFT calculations, were performed on corresponding cation radicals to get further insights into their electronic structures. The ground state optimized structures of 1-3*+ showed no visible changes in the structural parameters of the macrocycles, but the SOMO and LUMO orbitals were highly stabilized compared to the HOMO-LUMO of the parent macrocycles 1-3 (Figure 4a, S18-20). The SOMO and LUMO were present all over the structures 1-3°+ with negligible contribution from crowned moiety similar to that of the macrocycles 1-3. The LUMO was highly stabilized in cation radicals 1-3^{•+} compared to SOMO, leading to a significant decreasing of the SOMO-LUMO gap (~0.85 eV), which is almost half of that of the HOMO-LUMO gap (~2.2 eV) of macrocycles 1-3. Furthermore, TD-DFT studies on cation radicals 1-3^{•+} showed a new intense transition in the NIR region at ~1050 nm corresponding to $S \rightarrow$

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Figure 4. (a) Energy level diagrams of compound 2 and 2⁺⁺, (b) overlay of absorption and TD-DFT spectra of 2⁺⁺, (c) Spin density plot of 2⁺⁺.

L+1 and S-1 \rightarrow L electronic transitions, which indicates that the absorption band experienced massive bathochromic shift (~ 500 nm) upon formation of cation radicals 1–3^{•+} which is in agreement with the experimental observations (Figure 4b, S18– 20). The longest absorption predicted for 1–3^{•+} was found to be for S-1 \rightarrow L (~2100 nm) transition which is typical for radical cations. Further, spin density analysis was performed on the cation radicals 1–3^{•+} to ascertain the paramagnetic spin localization on the macrocyclic core and corresponding spin density plots are presented in Figure 4c, S21. The studies revealed that the paramagnetic spin was highly delocalized on the macrocyclic core consisting of two pyrrol[1,2-a]indole moieties along with the phenylene bridge and no contribution from crowned moiety. Overall, the DFT as well as TD-DFT studies corroborate with the experimental observations.

Conclusions

In conclusion, we synthesized phenylene-bridged bis-pyrrolo [1,2-a]indole crowned macrocycles 1–3 using readily synthesized precursors under mild reaction conditions. The X-ray structure revealed that the two pyrrolo[1,2-a]indole moieties were parallel to each other, and the pyrrolo[1,2-a]indole moieties were deviated by an angle which are in the range of $9.50^{\circ}-12.0^{\circ}$ from the mean plane defined by 28 macrocyclic core atoms. The pyrrolo[1,2-a]indole containing macrocycles 1–3 absorbs strongly in the visible region, electron-rich and undergoes oxidations readily. The macrocycles 1–3 readily formed stable cation radicals $1-3^{\circ+}$ upon treatment with TFA, which are stable for about a week in open air. The cation

radicals absorb in the NIR region, and the experimental observations were further validated by DFT and TD-DFT studies.

Experimental Section

General Information. The chemicals, such as BF₃·Et₂O and 2,3dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), were used as obtained from Aldrich. All other chemicals used for the synthesis were reagent grade unless otherwise specified. Column chromatography was performed on silica gel (100-200) and basic alumina. The ¹H and ¹³C NMR spectra were recorded in CDCl₃ on Bruker 400 and 500 MHz instruments. The frequencies for the ¹³C nucleus are 100.06 and 125.77 MHz for 400 and 500 MHz instruments, respectively. Tetramethylsilane [Si(CH₃)₄] was used as an internal standard for ¹H and ¹³C NMR. Absorption and steady-state fluorescence spectra were obtained with PerkinElmer Lambda-35. Cyclic voltammetry (CV) studies were carried out with BAS electrochemical system utilizing the three-electrode configuration consisting of glassy carbon (working electrode), platinum wire (auxiliary electrode) and saturated calomel (reference electrode) electrodes. The experiments were done in dry dichloromethane using tetrabutylammonium perchlorate as a supporting electrolyte. EPR spectra were recorded on a JEOL model FA200 electron spin resonance spectrometer. The HR-mass spectra were recorded with a Q-TOF micro mass spectrometer.

Computational Details: All the calculations were performed using the Gaussian 09 program package.^[28] The density functional theory (DFT) method, hybrid functional uB3LYP with basis set 6–31G (d,p),^[32,33] was used to optimizes the geometries of the phenylene bridged bis- pyrrolo[1,2-a]-indol crowned macrocycle 1–3 and their oxidized forms $1-3^{\bullet+}$ in their ground (S0) states. The minimum energies surface of the optimized geometries of 1-3 and $1-3^{\bullet+}$ were verified by vibrational analyses, and no imaginary frequencies were found. The vertical excitation energies and oscillator strengths

Chem Asian J. 2021, 16, 1–10 www.chemasianj.org 7 These are not the final page numbers! 7 were obtained for the 50 lowest S0 \rightarrow Sn transitions at the optimized S0 state equilibrium geometries using the time-dependent density functional theory (TDDFT) method that was carried out at the same level of theory.^[29-31] All the computations in the chloroform media were carried out using the self-consistent reaction field (SCRF) under the polarizable continuum model (PCM).^[30,31] The electronic absorption spectra, including wavelengths, were systematically investigated using TDDFT with the PCM model based on the optimized ground structure.

Synthesis of compound 1: A sample of diol 5 a (100 mg,0.20 mmol) and benzitripyrrane 6a (84 mg, 0.20 mmol) was dissolved in 150 ml of CH₂Cl₂ taken in a 250 ml of one necked round-bottom flask and purged nitrogen for 5 min. The condensation reaction was initiated by addition of BF₃.OEt₂ (2.5 µl, 0.02 mmol). After 10 minutes, the reaction mixture was oxidized by adding DDQ (114 mg, 0.50 mmol) and the reaction mixture was stirred in open air for additional 30 minutes. The solvent was removed under reduced pressure and the crude compound was purified by basic alumina column chromatography using petroleum ether-CH2Cl2 (40:60) and afforded pure macrocycle 1 as a violet solid in 15% yield (26 mg, 0.029 mmol). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, J=8.6 Hz, 2H), 7.59-7.44 (m, 8H), 7.30 (dd, J=10.8, 4.5 Hz, 7H), 7.23-7.17 (m, 3H), 7.14 (dd, J = 8.2, 1.6 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.83 (dd, J =13.1, 5.6 Hz, 2H), 6.81–6.75 (m, 2H), 6.58 (d, J=5.8 Hz, 1H), 6.54 (dd, J=8.7, 2.2 Hz, 1H), 6.08 (d, J=2.1 Hz, 1H), 5.44 (d, J=2.0 Hz, 1H), 4.13-3.98 (m, 2H), 3.95-3.81 (m, 1H), 3.61 (dd, J=18.3, 9.2 Hz, 3H), 3.56-3.48 (m, 1H), 3.44-3.35 (m, 1H), 2.42 (s, 9H), 2.29 (s, 3H) ¹³C NMR (126 MHz, CDCl₃) δ 155.4, 154.4, 143.7, 143.2, 140.8, 140.3, 138.8, 138.8, 138.2, 137.7, 137.3, 136.0, 135.0, 134.7, 134.5, 132.7, 132.5, 132.1, 131.9, 131.7, 131.6, 131.6, 131.4, 130.9, 130.6, 129.5, 129.4, 128.8, 128.0, 127.8, 126.5, 125.3, 124.2, 124.0, 121.5, 121.0, 120.6, 112.8, 111.9, 111.3, 107.9, 101.0, 98.0, 70.38, 68.8, 67.9,64.6,31.6,29.4,21.2.HRMS (ESI-TOF), m/z calculated for C₆₂H₅₀N₂O₃[[M]⁺ 870.3817, found 870.3817.

Synthesis of compound 2: Compound 2 was synthesized under similar reaction conditions used for compound 1 using the crown diol 5b (100 mg,0.188 mmol), benzitripyrrane 6a (78 mg, 0.187 mmol), $BF_3.OEt_2$ (2.3 µl, 0.018 mmol) and DDQ (107 mg, 0.47 mmol). The crude compound was purified by basic alumina column chromatography using petroleum ether-CH₂Cl₂ (30:70) and afforded compound 2 as a violet solid in 12% yield (19 mg,0.021 mmol). ¹H NMR (500 MHz, CDCl₃) δ 7.55 (dddd, J= 34.0, 15.6, 8.1, 1.7 Hz, 9H), 7.33-7.27 (m, 5H), 7.23-7.16 (m, 3H), 7.13 (dd, J = 8.2, 1.7 Hz, 1H), 7.02 (dd, J = 8.7, 2.0 Hz, 4H), 6.82 (q, J =5.6 Hz, 2H), 6.79–6.75 (m, 2H), 6.57 (d, J=5.8 Hz, 1H), 6.53 (dd, J= 8.7, 2.3 Hz, 1H), 6.08 (d, J=2.1 Hz, 1H), 5.44 (d, J=2.1 Hz, 1H), 4.14-4.05 (m, 1H), 4.01 (d, J=2.2 Hz, 1H), 3.97-3.88 (m, 1H), 3.87 (d, J= 0.8 Hz, 6H), 3.63 (dd, J=21.8, 6.1 Hz, 3H), 3.56-3.46 (m, 1H), 3.45-3.33 (m, 1H), 2.42 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 158.3, 155.4, 154.5, 143.5, 142.9, 140.9, 140.4, 138.8, 137.7, 137.2, 135.3,134.8, 134.9, 134.6, 134.5, 132.7, 132.4, 132.0, 131.4, 130.9, 130.6, 129.4, 129.2, 129.0, 128.9, 127.1, 126.6, 125.3, 123.9, 121.4, 120.9, 120.5, 114.4, 112.6, 111.8, 111.5, 111.3, 107.9, 101.0, 98.0, 70.3, 68.9, 67.9, 64.7, 55.3, 29.7, 21.3. HRMS (ESI-TOF), m/z calculated for C₆₂H₅₀N₂O₅ [M]⁺ 902.3714, found 902.3719.

Synthesis of compound 3: Compound 3 was synthesized under similar reaction conditions used for compound 1 using the crown and compound diol 5 b (100 mg,0.188 mmol) 6b (85 mg,0.189 mmol), BF₃.OEt₂ (2.3 μl, 0.018 mmol) and DDQ (107 mg, 0.47 mmol). The crude compound was purified by basic alumina column chromatography using petroleum ether-CH₂Cl₂ (20:80) and afforded macrocycle 3 as a violet solid in 10% yield (17 mg, 0.018 mmol). ¹H NMR (400 MHz, CDCl₃) δ 7.59 (ddd, *J*=31.3, 13.2, 9.0 Hz, 9H), 7.47 (d, J=8.3 Hz, 1H), 7.36-7.29 (m, 3H), 7.13 (d, J=8.2 Hz, 1H), 7.02 (d, J=7.0 Hz, 4H), 6.97-6.87 (m, 3H), 6.86-6.72 (m, 5H), 6.55 (dd, J=14.0, 3.9 Hz, 2H), 6.21 (d, 1H), 5.45 (d, J=1.7 Hz, 1H), 4.16–3.95 (m, 2H), 3.88 (s, 9H), 3.78 (s, 3H), 3.69–3.34 (m, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 155.71, 154.72, 144.01, 143.44, 141.14, 140.64, 139.13, 139.05, 138.46, 137.96, 137.54, 136.32, 136.23, 135.32, 134.95, 134.78, 132.98, 132.84, 132.43, 132.22, 132.12, 132.04, 131.94, 131.87, 131.69, 131.15, 130.85, 129.84, 129.14, 128.30, 128.09, 126.83, 125.58, 124.48, 124.27, 121.79, 121.25, 120.85, 113.14, 112.15, 111.64, 108.22, 101.29, 98.26, 70.62, 69.14, 68.16, 64.93, 21.51. HRMS (ESI-TOF), m/z calculated for C₆₂H₅₀N₂O₅ [M]⁺ 934.3617, found 934.3615.

Supporting Information

Supporting information contains characterization data (HRMS, ¹H, ¹³C NMR spectra), EPR, DFT calculation data and crystallographic characterization.

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Conflict of Interest

The authors declare no conflict of interest.

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- [1] M. M. Heravi, V. Zadsirjan, RSC Adv. 2020, 10, 44247–44311.
- [2] F. Salehian, H. Nadri, L. Jalili-Baleh, L. Youseftabar-Miri, S. N. Abbas Bukhari, A. Foroumadi, T. Tüylü Küçükkilinç, M. Sharifzadeh, M. Khoobi, *Eur. J. Med. Chem.* 2021, 212, 113034–113099.
- [3] K. R. A. Abdellatif, R. B. Bakr, Med. Chem. Res. 2021, 30, 31–49.
- [4] M. Tanaka, S. Sagawa, J. ichi Hoshi, F. Shimoma, K. Yasue, M. Ubukata, T. Ikemoto, Y. Hase, M. Takahashi, T. Sasase, N. Ueda, M. Matsushita, T. Inaba, *Bioorg. Med. Chem.* 2006, 14, 5781–5794.
- [5] K. A. Koo, N. D. Kim, Y. S. Chon, M. S. Jung, B. J. Lee, J. H. Kim, W. J. Song, Bioorg. Med. Chem. Lett. 2009, 19, 2324–2328.
- [6] N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* 2013, 18, 6620–6662.
- [7] J. Jampilek, Molecules 2019, 24, 3839-3843.
- [8] S. Tahlan, S. Kumar, B. Narasimhan, BMC Chem. Biol. 2019, 13, 1–21.
- [9] M. Toyota, M. Ihara, Nat. Prod. Rep. 1998, 15, 327-340.
- [10] T. R. Sutariya, B. M. Labana, N. J. Parmar, R. Kant, V. K. Gupta, G. B. Plata, J. M. Padrón, New J. Chem. 2015, 39, 2657–2668.
- [11] L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn, V. M. Avery, Org. Lett. 2009, 11, 329–332.
- [12] M. B. Johansen, M. A. Kerr, Org. Lett. 2008, 10, 3497-3500.
- [13] B. M. Trost, B. M. O'Boyle, W. Torres, M. K. Ameriks, Chem. A Eur. J. 2011, 17, 7890–7903.
- [14] S. A. Samsoniya, D. O. Kadzhrishvili, I. S. Chikvaidze, *Pharm. Chem. J.* 2011, 45, 22–25.
- [15] W. T. Bradner, Cancer Treat. Rev. 2001, 27, 35–50.
- [16] J. E. C. Tejeda, B. K. Landschoot, M. A. Kerr, Org. Lett. 2016, 18, 2142– 2145.
- [17] D. A. Gubler, R. M. Williams, Tetrahedron Lett. 2009, 50, 4265–4267.
- [18] J. F. Liu, Z. Y. Jiang, R. R. Wang, Y. T. Zheng, J. J. Chen, X. M. Zhang, Y. B. Ma, Org. Lett. 2007, 9, 4127–4129.





- [19] C. Lorton, A. Voituriez, Eur. J. Org. Chem. 2019, 2019, 5133–5150.
- [20] B. Ojha, K. Laxman, M. Ravikanth, Asian J. Org. Chem. 2021, 10, 857–867.
 [21] B. Ojha, A. Kumar, K. G. Thorat, M. Ravikanth, Tetrahedron 2019, 75, 130574.
- [22] R. Sengupta, K. G. Thorat, M. Ravikanth, J. Org. Chem. 2018, 83, 11794– 11803.
- [23] A. N. Cammidge, O. Öztürk, Tetrahedron Lett. 2001, 42, 355–358.
- [24] F. R. Kooriyaden, S. Sujatha, C. Arunkumar, Polyhedron 2017, 128, 85-94.
- [25] N. Nijegorodov, P. V. C. Luhanga, J. S. Nkoma, D. P. Winkoun, Spectrochim. Acta Part A 2006, 64, 1–5.
- [26] N. I. Nijegorodov, W. S. Downey, J. Phys. Chem. 2002, 98, 5639-5643.
- [27] L. Eberson, F. Radner, Acta Chem. Scand. 1991, 45, 1093–1095.
- [28] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, *Gaussian 09, Revis. A. 02; Gaussian, Inc Wallingford, CT, 2009* 2009.

- [29] J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 2005, 105, 2999–3094.
- [30] R. Bauernschmitt, R. Ahlrichs, Chem. Phys. Lett. 1996, 256, 454-464.
- [31] M. Cossi, V. Barone, R. Cammi, J. Tomasi, Chem. Phys. Lett. 1996, 255, 327–335.
- [32] W. J. Hehre, Acc. Chem. Res. 1976, 9, 399-406.
- [33] O. Treutler, R. Ahlrichs, J. Chem. Phys. 1995, 102, 346-354.

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FULL PAPER



A facile synthesis of electronically forma rich phenylene-bridged bis-pyrrolo radica

[1,2-a]indole crowned macrocycles 1-

3 is reported via intramolecular fusion

under oxidation conditions and

formation of corresponding cation radicals in the presence of TFA with huge bathochromic shift (~500 nm), leading to NIR (850–1400 nm) absorption. B. Ojha, Dr. K. Laxman, Prof. Dr. M. Ravikanth*

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Crowned Macrocycles Containing Two Pyrrolo[1,2-a] Indoles Created By Intramolecular Fusion