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PAPER

Ce^{III}-promoted oxidation. Efficient aerobic one-pot eco-friendly synthesis of oxidized bis(indol-3-yl)methanes and cyclic tetra(indolyl)dimethanes†Claudio C. Silveira,^{*a} Samuel R. Mendes,^b Marcos A. Villetti,^a Davi F. Back^a and Teodoro S. Kaufman^{*c}

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Indoles and benzaldehyde derivatives undergo an efficient one-pot smooth condensation and a further atmospheric-pressure aerobic dehydrogenation with CeCl₃ in *i*-PrOH, to afford the corresponding oxidized bis(indol-3-yl)methanes. Use of 2,2'-bisindole as the heterocyclic precursor provides cyclic tetra(indolyl)dimethane derivatives, which further undergo partial oxidation to the related calix-shaped macrocycles, carrying an all *cis* 1,3,7-cyclodecatriene core and supporting a 2,2'-biindolylidene moiety. The syntheses of these high value-added compounds is operationally simple and can be performed at room temperature under mild, neutral and environmentally friendly conditions.

Introduction

The indole scaffold is a prominent and privileged structural motif, widely found in numerous natural products and various synthetic compounds, which exhibit a range of important biological activities or bear technological interest. Therefore, facile access to complex indole derivatives is regarded as highly relevant.¹

The indole moiety is the basic unit of cyclic oligoindole derivatives. The few available examples reveal them as interesting synthetic targets due to their spectroscopic features, stacking interactions, self-association and conformational properties, as well as for their potential as ligands or ion-sensing scaffolds.² Among the cyclic tetrameric indoles (Fig. 1), the 5,6-dihydroxy-indole derivative **1** has been proposed to account for the structural and spectral properties of eumelanins, the black insoluble semiconductor biopolymers of human skin, hair and eyes, and a cyclic pentamer analog has been recently synthesized.^{3a-e} In addition, the symmetric cyclic tetra(indolyl)tetramethane compound **2** (CTet) was shown to possess antiproliferative activity, inducing G1 cell-cycle arrest.^{3f-h}

On the other hand, it was suggested that macrocyclic indoles **3** can be manipulated to promote molecular recognition and ion binding,^{4a} it was demonstrated that **4** and its congeners offer high selectivity towards different anions,^{2c,4b,c} and it was shown

that porphyrinoid **5** is able to bind Cu^{II}, Zn^{II} and Ni^{II} ions,^{4d} while cyclic tetraindole **6** has also been prepared, as an analog of the natural plant growth regulator and antitumor agent caulerpin.^{2d,4e,f}

The synthesis of stable conformers of the sulfur-bridged cyclic tetraindole structure **7**,^{5a} the preparation of macrocycle **8**^{5b} and the regiocontrolled Rh^{II}-carbenoid mediated synthesis of indolophanes **9** have also been reported; among the latter, changing the length of the spacer resulted in modifications of the shape and size of the cavity.^{5c} Interestingly, the seemingly complex calix[4]indole **10** was synthesized by a facile acid-catalyzed tetramerization of the corresponding 7-hydroxymethyl indole.^{2a}

The indole motif is also present in bis(indol-3-yl)methanes (BIMs) and in their oxidized derivatives, which are useful as dyes^{6a-c} and colorimetric chemosensors.^{6d-g}

BIMs have been synthesized in moderate to very good yields by condensation of indoles and aldehydes in the presence of a wide range of promoters, including Ce(NH₄)₂(NO₃)₆ (CAN), I₂, H₄[Si(W₃O₁₀)₃], ion-exchange resins, zeolites, montmorillonite-K10, ionic liquids, InF₃, InCl₃, In(OTf)₃, LiClO₄, NBS and CuBr, among others.⁷ However, to date, the preparation of oxidized BIMs requires an additional reaction step from the corresponding BIMs, which has been invariably reported to take place in low to moderate yields. Currently, conditions for the synthesis of oxidized BIMs are restricted to Fe^{III} oxidation^{6b} and dehydrogenation with single-electron oxidants such as TCQ or DDQ.^{8a-c} Noteworthy, oxidizing conditions involving peroxidic reagents such as (*t*-BuO)₂, TBHP and PhCOOO-*t*-Bu do not yield oxidized BIMs.^{8d}

We have recently disclosed the synthesis of BIMs using CeCl₃·7H₂O/glycerol as a recyclable catalytic system.⁹ In view of our interest in the development of new, more efficient and cleaner methods for classical transformations and new applications of Ce^{III} in organic synthesis,¹⁰ and taking into account the unique redox properties of the Ce^{III}/Ce^{IV} pair, we decided to

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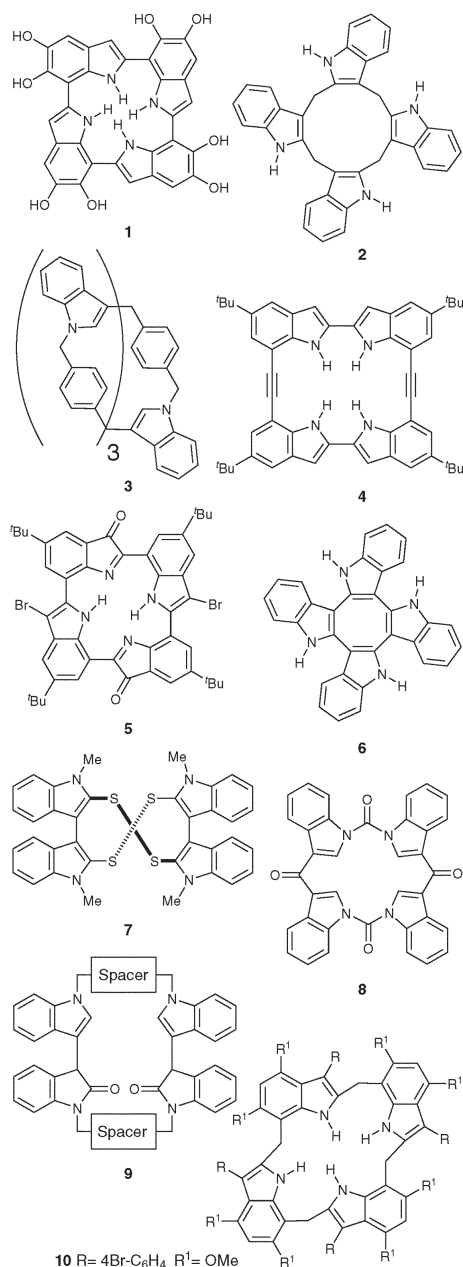


Fig. 1 Representative examples of cyclic tetraindolyl derivatives.

develop suitable conditions for a Ce^{III} -mediated one-pot access to oxidized BIMs and cyclic tetra(indolyl)dimethanes.

It has been shown that the reaction of 3-alkyl indoles with IBX under CeCl_3 promotion afforded products other than 3-methyleneindolenines^{11a} and that $\text{Ce}(\text{AcO})_3/\text{TBHP}$ promotes the oxidative functionalization of indoles at C3.^{11b} On the other hand, recent reports provide information on the use of the $\text{CeCl}_3/i\text{-PrOH}$ system as an efficient promoter for the α -hydroxylation of 1,3-dicarbonylic moieties, in the presence of air as a source of dioxygen,¹² and the group of Maiti disclosed the use of the $\text{VO}(\text{acac})_2\text{-CeCl}_3$ reagent for the aerobic synthesis of glycal-based chiral benzimidazoles.¹³

Therefore, and taking into account that physiological dehydrogenation of 3-methylindole by cytochrome P450 is a two-step

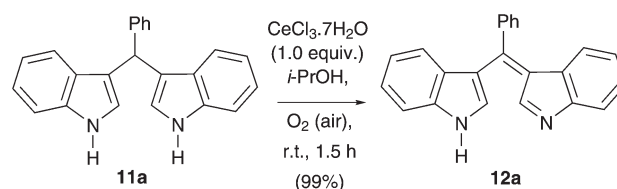
radical process in which a 3-methyl radical is formed first, followed by a second one-electron oxidation affording the imine-methide (3-methylene indolenine) species,¹⁴ we hypothesized that Ce^{III} could promote a mild radical reaction leading to oxidized BIMs, using molecular oxygen as the final oxidant.

Aerobic oxidation processes are attractive because they employ molecular oxygen, the most available and renewable oxidant, and therefore is the terminal oxidant of choice from an economic and ecological point-of-view. They are also atom-efficient and produce water as a reaction by-product. Due to its ready accessibility, safety issues and convenience of use, the synthetic process gains additional value when pure dioxygen can be replaced with atmospheric air.¹⁵

Results and discussion

Our initial expectations were fulfilled, in an exploratory test, when the stirring of a mixture of BIM **11a** and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.0 equiv.) in *i*-PrOH under air at room temperature for 1.5 hours, afforded 99% of a more polar product, to which structure **12a** was assigned based on its NMR spectral data analysis (Scheme 1). The key role of $\text{Ce}(\text{III})$ became clear when a control experiment, without the promoter, was left under stirring for 1 hour and the production of **12a** was not observed. Only after addition of the cerium salt did the solution turn reddish and product generation was observed.

Single crystal X-ray analysis of **12a** (Fig. 2) confirmed the proposed structure. The observed dihedral angles $\text{C1-C2-C10-C2}^\#$, C1-C2-C10-C11 , and C12-C11-C10-C2 were -20.53° , 159.47° and 120.34° , respectively, with similar bond lengths for C2-C10 and $\text{C2}^\#\text{-C10}$ (1.4076 Å).¹⁶ The small torsion angle observed between both indole moieties, which has also been found in Cu^{II} complexes of oxidized BIMs,^{8b} avoids steric repulsion between H-C1 and $\text{H-C1}^\#$.



Scheme 1 Air-mediated room temperature oxidation of BIM **11a** promoted by $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in *i*-PrOH.

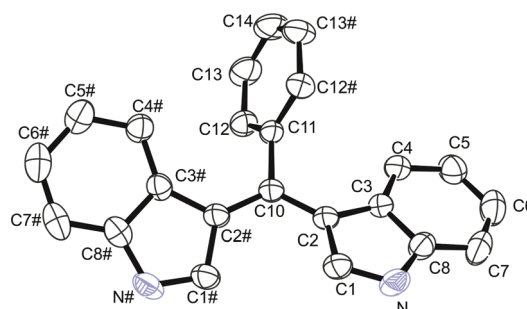
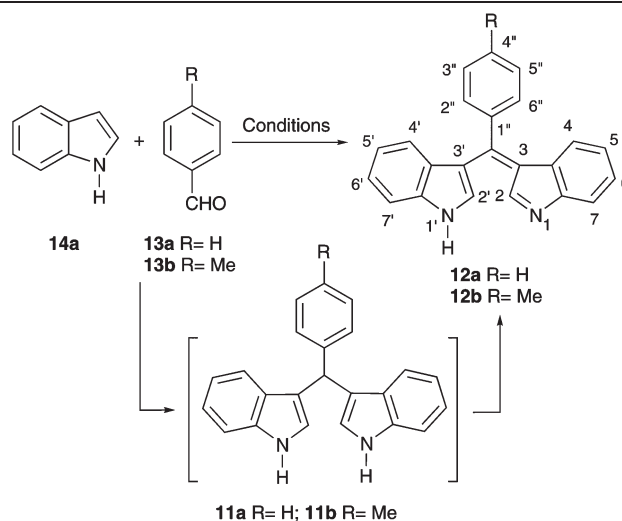


Fig. 2 X-Ray crystal structure of the oxidized BIM product **12a**.

Table 1 Optimization of the one-pot synthesis of oxidized BIMs (**12**)

Entry no.	R	Promoter (no. equiv.)	Oxidant	Solvent	Time (h)	Yield (%)
1	H	CeCl ₃ ·7H ₂ O (1.0)	Air	i-PrOH	5.0	69
2	Me	CeCl ₃ ·7H ₂ O (1.0)	Air	i-PrOH	5.0	72
3	Me	CeCl ₃ ·7H ₂ O (0.5)	Air	MeNO ₂	24	—
4	Me	CeCl ₃ ·7H ₂ O (0.5)	Air	PEG400	24	30 ^a
5	Me	CeCl ₃ ·7H ₂ O (0.5)	Air	MeCN	24	—
6	Me	CeCl ₃ ·7H ₂ O (0.5)	Air	Glycerol	24	95 ^a
7	Me	Anh. CeCl ₃ (1.0)	Air	i-PrOH	1.5	98
8	H	Anh. CeCl ₃ (1.0)	Air	EtOH	3.5	98
9	H	Anh. CeCl ₃ (1.0)	Air	MeOH	5.0	95
10	H	Anh. CeCl ₃ (1.0)	Air	<i>t</i> -BuOH	7.0	93
11	Me	Anh. CeCl ₃ (2.0)	Air	i-PrOH	1.5	98
12	Me	Anh. CeCl ₃ (0.5)	Air	i-PrOH	5.0	69
13	Me	Anh. CeCl ₃ (0.1)	Air	i-PrOH	5.0	49
14	Me	Anh. CeCl ₃ (1.0)	Dioxygen	i-PrOH	1.25	97
15	H	CAN (1.0)	Air	i-PrOH	3.0	— ^b

^a Isolated yields of the BIM product. ^b No product (BIM/oxidized BIM) was observed.

The high efficiency and extreme simplicity of this new reaction, together with the known ability of CeCl₃·7H₂O to promote the formation of BIMs,⁹ prompted us to explore the possibility of performing the transformation as a one-pot process, from benzaldehyde derivatives and indoles.

To our delight, subjecting a mixture of benzaldehyde (**13a**, 0.5 mmol) and indole (**14a**, 1.0 mmol) to reaction with 1.0 equiv. of CeCl₃·7H₂O, at room temperature, resulted in 69% of **12a** after 5 hours (Table 1, entry 1).

Analogously *p*-tolualdehyde (**13b**) furnished 72% of **12b** (Table 1, entry 2). TLC monitoring of the reaction indicated the formation of an intermediate, which was isolated and identified as the corresponding bis(indol-3-yl)methane **11b**.

In view of these promising results, a systematic investigation was carried out in order to examine the effects of the reaction solvent, source of dioxygen and amount of catalyst on the product yields. Use of glycerol or PEG 400 only afforded the 3,3'-bis(indol-3-yl)methane **11b**, and no reaction was detected in MeCN and MeNO₂ (Table 1, entries 3–6).

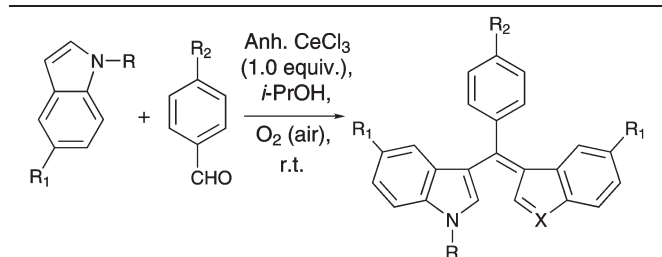
In addition, it was observed that the use of anhydrous CeCl₃¹⁷ dramatically reduced the reaction time to 1.5 h, while increasing

the yield of **11b** to 98% (Table 1, entry 7). Under these conditions, other low molecular weight alcohols could also be employed as solvents; however, longer reaction times were required for the transformation to reach completion (Table 1, entries 8–10).

The performance of the reaction was also tested in the presence of over- and sub-stoichiometric amounts of CeCl₃. Addition of the promoter in excess did not improve the reaction performance (Table 1, entry 11), while use of sub-stoichiometric amounts of CeCl₃ afforded lower yields of product after longer reaction times (Table 1, entries 12 and 13).

Interestingly enough, only a small decrease in the required reaction time was achieved by carrying out the reaction in a pure molecular oxygen atmosphere (Table 1, entry 14), while quite surprisingly, the use of CAN as a source of cerium did not afford the expected BIM¹⁸ when i-PrOH was employed as solvent (Table 1, entry 15).

Therefore, it was concluded that the optimum reaction performance was obtained when a solution of the reactants and 1.0 equiv. of anhydrous CeCl₃ in i-PrOH was vigorously stirred at room temperature, under air. The established protocol was

Table 2 Air-mediated one pot synthesis of oxidized BIMs **12a–f**

Entry no.	Product no.	R	R ₁	R ₂	X	Time (h)	Yield ^a (%)
1	12a	H	H	H	N	2.0	96
2	12b	H	H	Me	N	2.0	98
3	12c	H	H	Cl	N	5.0	93
4	12d	H	H	OMe	N	2.0	97
5	12e	Me	H	OMe	N ⁺ -Me	3.0	91
6	12f	H	<i>p</i> -Tolyl	OMe	N	4.0	89

^a Isolated yields of the oxidized BIM product.

applied to other indoles (Table 2), including *N*-methylindole (Table 2, entry 5) and 5-(*p*-tolyl)indole (Table 2, entry 6), and different benzaldehyde derivatives.

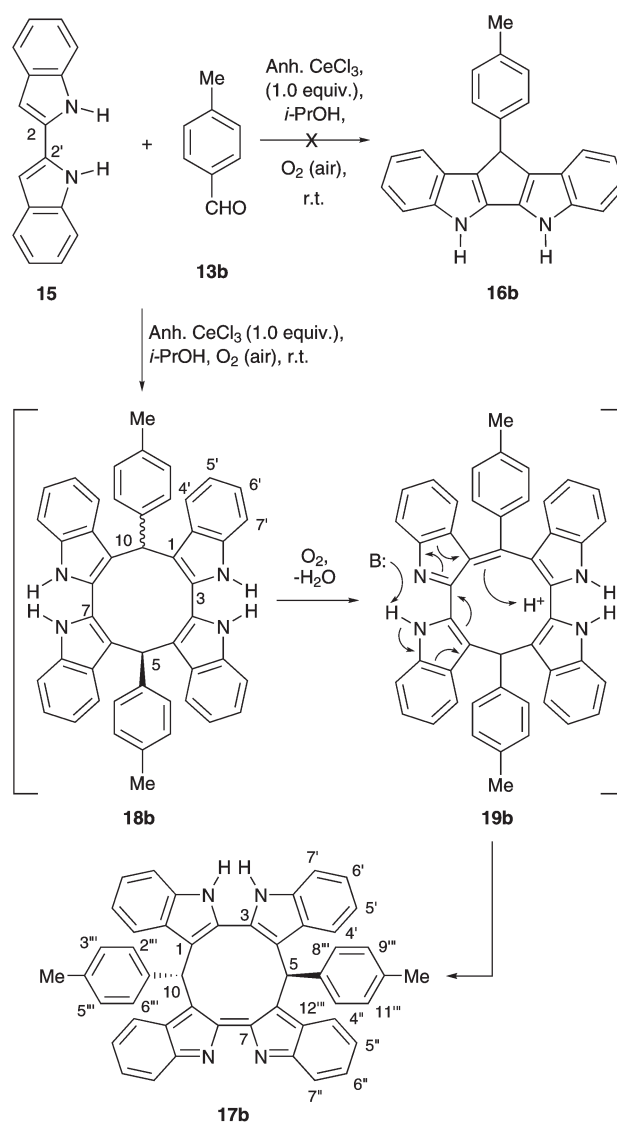
In all cases, the oxidized BIMs (**12a–f**) were obtained in excellent yields after stirring at room temperature for 2.0–4.0 h. Notably, however, the reaction with *p*-chlorobenzaldehyde took more time to undergo completion towards **12c**,¹⁹ mainly due to a slower oxidation step, as revealed by TLC monitoring of the transformation. On the other hand, *N*-methylindole gave the quaternarized product **12e**.

Encouraged by the results of the transformations involving simple indoles, and with the aim of expanding the scope of this Ce^{III}-based reaction, the study of the behavior of 2,2'-bisindole (2,2'-bisindolyl, **15**) as the starting indole component was undertaken.

Literature precedents indicate that in bi-indole derivatives carrying a spacer between both indolyl moieties, the intramolecular condensation of the indole with aldehydes is favored over the intermolecular alternative.^{20a–c} However, reaction of **13b** with **15** under the previously established conditions towards oxidized BIMs did not afford the expected product **16b**^{20d} (Scheme 2).

Instead, the 10-membered ring 2,2'-biindolylidene derivative **17b**, bearing a 1,3,7-cyclodecatriene core was obtained. Most probably, the product resulted from connection of the two molecules of the bis-indole scaffold with a pair of methine bridges provided by the aldehyde, through the intermediacy of the cyclic derivative **18b**. Interestingly enough, isomeric cyclodecatrienes like the pregeijerenes A and B have been isolated from *Pimpinella cumbrae* Link, *Amyris diatrypa*, *Chromolaena odorata* and *Juniperus erectopatens*, among others.²¹

Compounds **17** and **18** can be accessed as *syn* and *anti* diastereomers, the former having C_{2v} symmetry. Despite both possible diastereomers of **18b** [**18b1** (*syn*) and **18b2** (*anti*)] being concomitantly formed (in different proportions) during the condensation step, only one diastereomer of **17b** is produced after the dehydrogenation of the diastereomeric intermediates, probably the result of a process involving the formation of a BIM-type

**Scheme 2** Synthesis of the oxidized cyclic indolylmethane **17b**.

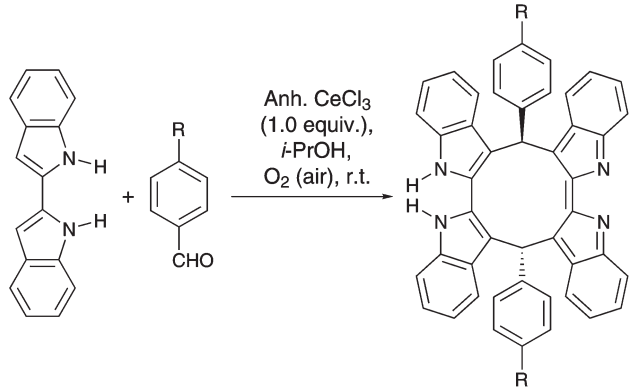
product (**19b**), followed by double bond rearrangement of this partially oxidized BIM intermediate. The structures of the tetra (indolyl)dimethanes **17b** and **18b** were unambiguously established by spectroscopic (NMR) and GC-MS means.

Re-examination of the reaction conditions revealed that *i*-PrOH outperformed glycerol, MeNO₂ and MeCN as solvents, while the 1 : 1 : 1 molar stoichiometry between 2,2'-bisindole, aldehyde and CeCl₃ furnished the best product yields.

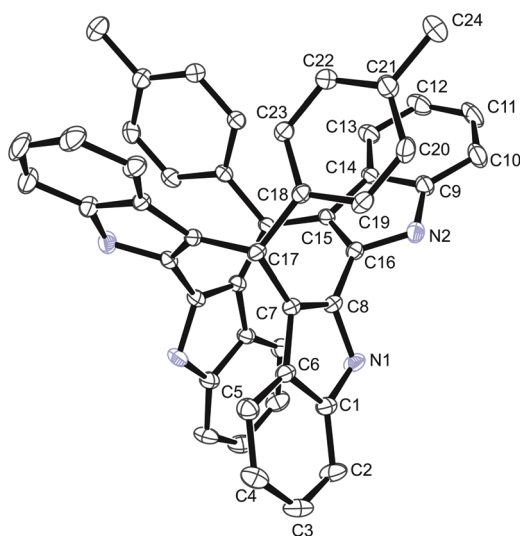
The design and synthesis of macrocycles containing aromatic/heteroaromatic ring systems constitute an intriguing branch of organic and supramolecular chemistry; therefore, the scope of the transformation was extended to some other aldehydes under these optimized conditions (Table 3).

The observed results were very similar to those achieved in the reactions with indole, except that the oxidation was slower and longer reaction times were required (7.5 to 11.0 h).

The reaction times and product yields were well correlated to the structure of the starting aldehyde, with the *p*-chlorobenzaldehyde derivative **17c** isolated in the lowest yield, also being the

Table 3 Synthesis of cyclic oxidized tetra(indolyl)dimethanes **17a–d**


Entry no.	Product no.	R	Time (h)	Isolated yield (%)
1	17a	H	9.0	62
2	17b	Me	8.0	67
3	17c	Cl	11.0	53
4	17d	OMe	7.5	69

**Fig. 3** X-Ray molecular conformation of the major diastereomer of tetra(indolyl)dimethane intermediate **18b1**.

more reluctant to undergo cyclization and subsequent dehydrogenation (Table 3, entry 3). Interestingly, the oxidized macrocycles **17** did not undergo further transformation under the $\text{CeCl}_3\text{-O}_2/i\text{-PrOH}$ system nor when submitted to the more conventional DDQ/MeCN oxidation conditions. This could be a result of the high strain suffered by the macrocycle. Medium-sized ring compounds (eight to eleven members) are among the most strained cycles. In addition, the strain of these 10-membered macrocycles (**17a–d**) is exacerbated by the presence of 8 sp^2 carbon atoms.

Attempts to obtain suitable crystals of compounds **17** for X-ray structure analysis were unsuccessful. However, the X-ray crystal structure of **18b1**, the major diastereomer of intermediate **18b** (Fig. 3), unequivocally confirmed the cyclic nature of the

products. Its crystal structure also evidenced the *syn* orientation of both tolyl moieties and the half-chair–boat–half-chair conformation of the 1,3,6,8-cyclodecatetraene core, exhibiting a “twisted saddle” form²² and allowing an all *cis* configuration of the double bonds, yielding an overall molecular shape of a cup, reminiscent of that of the calix[4]indoles.^{2a}

This arrangement, which lacks intra-annular hydrogens, has two bis-indole moieties embraced together through methine bridges. These bis-indole moieties in **18b** adopt *cisoid* conformations with N1–C8–C16–N2 torsion angles of 69.5° . Each bis-indole moiety has a chiral axis and both axes bear the same configuration. In this way, two alternate indole fragments establish themselves in a quasi-parallel orientation (the angle formed between both planar moieties is 12.5°), while the remaining pair of heterocyclic fragments point away from each other, forming an angle between their planes of 93.9° .

Each half of the molecule of **18b1** can be defined by two planes; one through atoms C16, C8, C7 and C17' and one through atoms C8, C16, C15 and C17. The two planes are inclined at an angle of 74.1° to each other. The C15–C17 and C7/C17 bonds are equivalent within experimental error, while the C8–C16 distance is that of a standard $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^2)$ single bond (1.47 Å).

On the other hand, the methinic hydrogens of **17b**, observed as a singlet resonating at δ_{H} 5.49 ppm, suggested their stereochemical assignment as *anti* and confirmed the proposed cyclic structure for these partially oxidized tetraindoles.

Employing the synthesis of **12a** as an example, a two-stage (condensation-oxidation) reaction mechanism for this one-pot transformation can be proposed (Scheme 3). In the first stage, the mode of action of CeCl_3 follows the general pattern of activity of other Lewis and protic acids which catalyze the synthesis of BIMs.²³

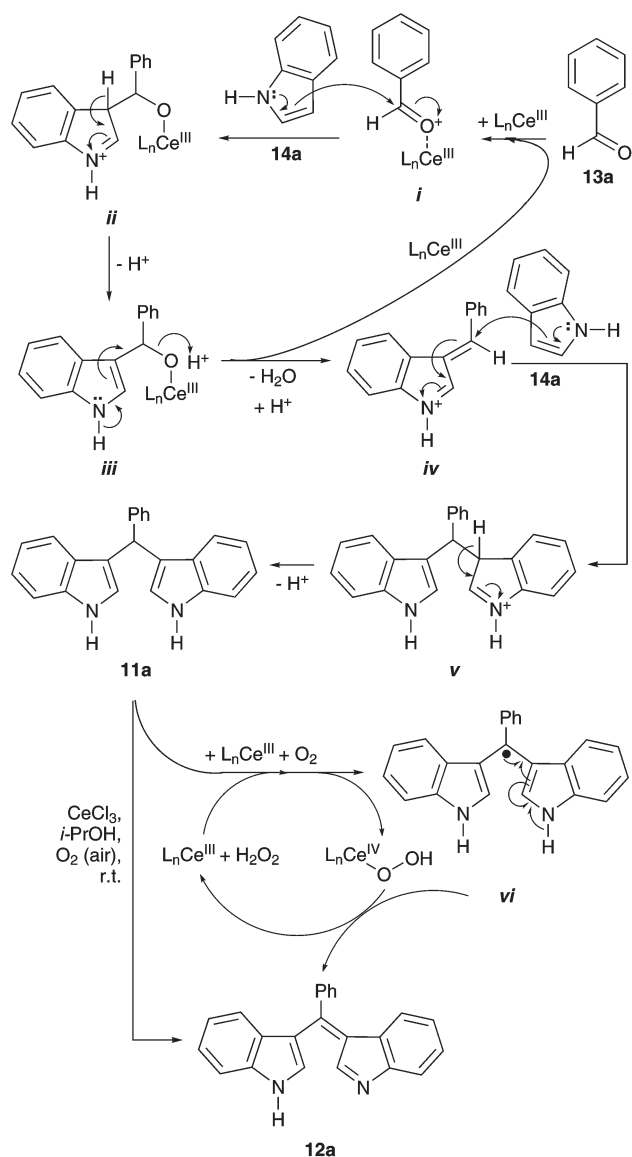
Upon Ce^{III} -activation of the carbonyl moiety (*i*) of the aldehyde (**13a**), the reaction with indole (**14a**) should produce the corresponding azafulvene through the intermediacy of Lewis acid coordinated species like *ii* and *iii*. Concomitantly, water is produced as a result of the condensation and the Ce^{III} promoter is liberated, entering again in the catalytic cycle.

Protonation of the azafulvene yields the azafulvenium ion *iv*, which, in turn, reacts with a second indole molecule to form the bis(indol-3-yl)methane (**11a**),²⁴ through the intermediacy of an indolinium derivative (*v*).

A detailed picture of the following oxidation stage of **11a** towards the related oxidized BIM (**12a**) is still unclear. However, mechanistic images can be drawn taking into account that under assistance of the promoter and in the presence of dioxygen, the abstraction of the activated methinic hydrogen of the BIM is very likely to take place, yielding *vi*, a very stable radical intermediate (or a carbocation by further oxidation) and a Ce^{IV} species.

The driving force of conjugation would then allow the latter to perform a second hydrogen abstraction (or a deprotonation), furnishing **12a** and releasing H_2O_2 together with the promoter as a Ce^{III} species, which can re-enter into the cycle. The so formed hydrogen peroxide could further participate in this transformation^{11b} and/or ultimately decompose to water.

Incorporation of aromatic heterocyclic systems into extended organic π systems is driven by the intriguing electronic and



Scheme 3 Proposed two-stage reaction mechanism for the one-pot Ce^{III} -promoted room temperature aerobic synthesis of oxidized bis(indol-3-yl)methane derivative **12a** from benzaldehyde (**13a**) and indole (**14a**) through the intermediacy of BIM **11a**.

photophysical properties of the resulting products.^{6c} These properties have also been studied in natural indole derivatives²⁵ bearing these characteristics.^{3a-c}

Therefore, the room temperature photoluminescent properties of the oxidized BIMs, including **17a**, were also studied (Table 4). The determinations were performed in DMSO due to the much lower solubility of the BIMs in other solvents; however, no spectral shifts were detected when the compounds were dissolved in EtOAc or CH_2Cl_2 .

It was observed that the UV-visible spectra exhibited absorption bands in the 280–300 nm region. The relatively high values of the molar absorptivity coefficient and absence of a solvent-mediated spectral shift effect suggested that the absorption could be attributed to a $\pi-\pi^*$ excitation.

Compounds **12a–c** exhibited their excitation maxima at 287 ± 1 nm ($\log \epsilon = 3.87 \pm 0.05$), while **12f** displayed a bathochromic

Table 4 UV-Vis and fluorescence characteristic maxima of the indole derivatives **12a–c**, **12f** and **17a**^a

Entry no.	Comp. no.	UV-vis $\lambda_{\text{max}}/\text{nm}$ ($\log \epsilon$)	Fluorescence ($\lambda_{\text{max}}/\text{nm}$)
1	12a	286 (3.92)	345; 406sh
2	12b	288 (3.82)	347
3	12c	288 (3.70)	—
4	12f	301 (3.93)	363
5	17a	353 (4.49)	447

^a Samples were dissolved in DMSO for UV (1.5×10^{-4} M) and fluorescence (1.5×10^{-5} M) determinations.

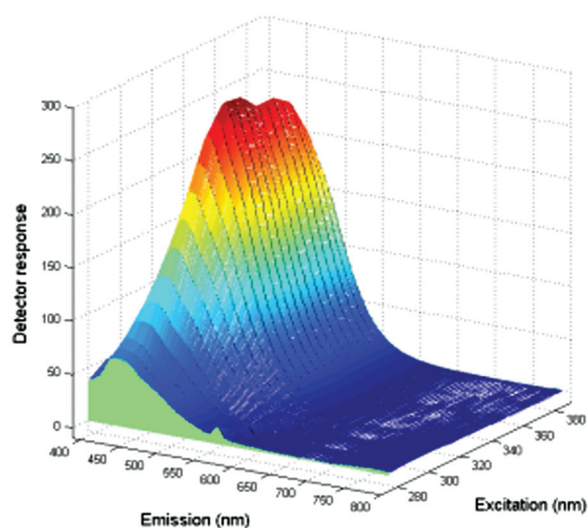


Fig. 4 Fluorescence spectrum of a 1.5×10^{-5} M solution of cyclic oxidized tetra(indolyl)dimethane **17a** in DMSO.

shift of the maximum of almost 15 nm ($\lambda_{\text{max}} = 301$ nm), as a consequence of its most extended conjugated system.

The fluorescence spectra of **12a,b** exhibited maxima at 345 nm, while that of **12f** showed an emission maximum at 363 nm. Interestingly, however, **12c** did not exhibit fluorescence, probably due to the presence of the chlorine atom in the molecule.

Among the cyclic compounds, the luminiscent properties of **17a** were verified (Fig. 4). This partially oxidized tetra(indolyl)dimethane derivative exhibited an ideal excitation wavelength of 353 nm ($\log \epsilon = 4.49$) with an emission maximum in the visible region of the spectrum (447 nm).

Conclusions

In conclusion, we have developed a very simple and highly efficient methodology for the synthesis of oxidized bis(indol-3-yl)methanes and partially oxidized cyclic tetra(indolyl)dimethane derivatives, carrying various functional groups, which involves a new application of Ce^{III} in organic synthesis and features the utilization of dioxygen as oxidant. To the best of our knowledge, this report is the first convenient one-pot process for the synthesis of these heterocycles and entails the first

preparation of oxidized BIMs using molecular oxygen from air as the oxidant.

This process, which uses a benign solvent (*i*-PrOH) and non-toxic and inexpensive CeCl_3 as the pre-catalyst, can be regarded as environmentally benign, eco-conscious and optimal with respect to economic issues.

Furthermore, the synthesis takes place at room temperature, from commercially available precursors, and the products are obtained in good to excellent yields. No precautions need to be taken to exclude moisture from the reaction medium.

This contribution should pave the way for the ready construction of more complex oxidized BIMs and partially oxidized cyclic tetra(indolyl)dimethanes, to unlock their potential applications as bioactive compounds, novel functional materials for selective sensors, or as emission layers for organic light-emitting diodes in microelectronics.²⁶

Experimental section

General information

Melting points were taken on MQAPF-301 melting point apparatus and are reported uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 (400 MHz) spectrometer, with the samples dissolved in $\text{DMSO}-d_6$; marked assignments (* or #) may be exchanged. IR spectra were recorded on a Shimadzu Prestige 21 FT-IR spectrophotometer, with the samples as KBr pellets. Low resolution mass spectra were run on a Shimadzu GCMS-QP2010 Plus mass spectrometer. High-resolution mass spectral data were obtained in a Bruker microTOF-Q IIT instrument, employing sodium formate as reference. X-Ray diffraction data were acquired with a Bruker Kappa APEX II CCD diffractometer, fit with a graphite monochromator and a $\text{Mo-K}\alpha$ radiation source ($\lambda = 0.71073 \text{ \AA}$). Excitation-emission spectra were obtained with a Varian Cary Eclipse spectrofluorometer, employing 1 cm quartz cuvettes. UV-visible spectra were taken with a Cary 50 Bio spectrometer, employing 1 cm quartz cuvettes. All reagents for synthesis were obtained commercially and used without further purification. Chromatographic purification was conducted by column chromatography using 60–120 mesh silica gel. Reaction progress was monitored by thin layer chromatography on Merck silica gel 60 F_{254} plates using UV light (254 and 360 nm) for detection.

Typical procedure for the synthesis of oxidized bis(indol-3-yl)-methanes (12)

Anhydrous CeCl_3 (0.246 g, 1.0 mmol) was added to a solution of indole (**14**, 1.0 mmol) and the benzaldehyde derivative (**13**, 0.55 mmol) in *i*-PrOH (3 mL), and the reaction was stirred at room temperature until all the starting material was consumed (TLC). Then, the solvent was evaporated under reduced pressure and the residue was purified by rapid filtration through a short column filled with silica gel (EtOAc/MeOH , 90:10, v/v), furnishing the corresponding product **12**.

3-[(1*H*-Indol-3-yl)(phenyl)methylene]-3*H*-indole (12a). M.p.: 210 °C (dec); IR (KBr, ν): 3417, 1543, 1485, 1411, 1199, 1122, 744 and 702 cm^{-1} ; ^1H NMR (δ): 6.67 (d, $J = 7.8$, 2H, 7-H and

7'-H), 7.04 (t, $J = 7.8$, 2H, 5-H and 5'-H), 7.30 (t, $J = 7.8$, 2H, 6-H and 6'-H), 7.57 (d, $J = 7.3$, 2H, 3''-H and 5''-H),* 7.63 (t, $J = 7.3$, 2H, 2''-H and 6''-H),* 7.68 (d, $J = 7.8$, 2H, 4-H and 4'-H), 7.77 (t, $J = 7.3$, 1H, 4''-H) and 8.36 (s, 2H, 2-H and 2'-H); ^{13}C NMR (δ): 115.7, 121.4, 122.6, 123.9, 125.7, 127.8, 129.5, 132.2, 132.6, 139.2, 143.0, 147.4 and 162.8; EI-MS (m/z , rel. int., %): 320 (M^+ , 33), 291 (7), 243 (5), 158 (8), 84 (70), 66 (100) and 46 (22); HRMS found m/z 321.1379; $\text{C}_{23}\text{H}_{17}\text{N}_2$ [($\text{M} + \text{H}$)⁺] requires m/z 321.1386.

3-[(1*H*-Indol-3-yl)(4-methyl-phenyl)methylene]-3*H*-indole (12b). M.p.: 202 °C (dec); IR (KBr, ν): 3390, 1628, 1481, 1408, 1199, 1123 and 752 cm^{-1} ; ^1H NMR (δ): 2.53 (s, 3H, 4''-Me), 6.75 (d, $J = 7.8$, 2H, 7-H and 7'-H), 7.12 (t, $J = 7.8$, 2H, 5-H and 5'-H), 7.35 (t, $J = 7.8$, 2H, 6-H and 6'-H), 7.49 (d, $J = 8.0$, 2H, 2''-H and 6''-H),* 7.55 (d, $J = 8.0$, 2H, 3''-H and 5''-H),* 7.77 (d, $J = 7.8$, 2H, 4-H and 4'-H), 8.51 (s, 2H, 2-H and 2'-H) and 14.64 (s, 1H, NH); ^{13}C NMR (δ): 21.8, 115.0, 121.5, 121.7, 124.5, 125.9, 127.2, 130.4, 133.4, 135.8, 140.4, 144.8, 147.0 and 169.3; EI-MS (m/z , rel. int., %): 334 (M^+ , 70), 333 (100), 317 (7), 291 (9), 243 (10), 159 (14) and 132 (7); HRMS found m/z 335.1545; $\text{C}_{24}\text{H}_{19}\text{N}_2$ [($\text{M} + \text{H}$)⁺] requires m/z 335.1543.

3-[(1*H*-Indol-3-yl)(4-chloro-phenyl)methylene]-3*H*-indole (12c). M.p.: 148 °C (dec); IR (KBr, ν): 3360, 1632, 1481, 1408, 1199, 1123 and 752 cm^{-1} ; ^1H NMR (δ): 6.74 (d, $J = 7.8$, 2H, 7-H and 7'-H), 7.12 (t, $J = 7.8$, 2H, 5-H and 5'-H), 7.34 (t, $J = 7.8$, 2H, 6-H and 6'-H), 7.64 (d, $J = 8.2$, 2H, 3''-H and 5''-H),* 7.72 (d, $J = 8.2$, 2H, 2''-H and 6''-H),* 7.77 (d, $J = 7.8$, 2H, 4-H and 4'-H) and 8.51 (s, 2H, 2-H and 2'-H); ^{13}C NMR (δ): 114.7, 120.8, 121.3, 123.9, 125.3, 126.5, 129.2, 133.9, 136.9, 137.8, 140.6, 146.8 and 164.6; EI-MS (m/z , rel. int., %): 356 [($\text{M} + 2$)⁺, 22], 354 (64), 353 (100), 317 (11), 291 (17), 243 (15), 159 (35) and 132 (19); HRMS found m/z 355.1003; $\text{C}_{23}\text{H}_{16}\text{ClN}_2$ [($\text{M} + \text{H}$)⁺] requires m/z 355.0997.

3-[(1*H*-Indol-3-yl)(4-methoxy-phenyl)methylene]-3*H*-indole (12d). M.p.: 213 °C (dec); IR (KBr, ν): 3394, 1597, 1481, 1411, 1203, 1126 and 752 cm^{-1} ; ^1H NMR (δ): 3.96 (s, 3H, 4''-OMe), 6.84 (d, $J = 7.8$, 2H, 7-H and 7'-H), 7.13 (t, $J = 7.8$, 2H, 5-H and 5'-H), 7.24 (d, $J = 8.7$, 2H, 3''-H and 5''-H), 7.36 (t, $J = 7.8$, 2H, 6-H and 6'-H), 7.63 (d, $J = 8.7$, 2H, 2''-H and 6''-H), 7.78 (d, $J = 7.8$, 2H, 4-H and 4'-H), 8.45 (s, 2H, 2-H and 2'-H) and 14.58 (s, 1H, NH); ^{13}C NMR (δ): 55.8, 114.4, 114.8, 120.8, 120.8, 123.6, 125.2, 126.7, 130.0, 135.8, 139.8, 146.1, 164.2 and 167.9; EI-MS (m/z , rel. int., %): 350 (M^+ , 88), 349 (100), 334 (15), 305 (55), 278 (12), 243 (12), 159 (10), 91 (30) and 43 (73); HRMS found m/z 351.1489; $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}$ [($\text{M} + \text{H}$)⁺] requires m/z 351.1492.

3-[(1-Methyl-1*H*-indol-3-yl)-(4-methoxy-phenyl)-methylene]-1-methyl-3*H*-indolium (12e). M.p.: 112 °C (dec); IR (KBr, ν): 3417, 1655, 1608, 1508, 1462, 1369, 1327, 1242, 1119 and 741 cm^{-1} ; ^1H NMR (δ): 3.98 (s, 3H, 4''-OMe), 4.13 (s, 6H, NMe), 6.86 (d, $J = 7.8$, 2H, 7-H and 7'-H), 7.21 (t, $J = 7.8$, 2H, 5-H and 5'-H), 7.26 (d, $J = 8.7$, 2H, 3''-H and 5''-H), 7.46 (t, $J = 7.8$, 2H, 6-H and 6'-H), 7.66 (d, $J = 8.7$, 2H, 2''-H and 6''-H), 7.82 (d, $J = 7.8$, 2H, 4-H and 4'-H) and 8.68 (s, 2H, 2-H and 2'-H); ^{13}C NMR (δ): 34.5, 55.8, 112.7, 114.9, 119.3, 120.8, 124.2, 125.3, 126.8, 129.9, 135.6, 140.0, 148.7, 164.3 and

166.6; EI-MS (m/z , rel. int., %): 379 (M^+ , 57), 378 (100), 364 (24), 319 (11), 271 (58), 249 (12), 159 (11) and 77 (5); HRMS found m/z 379.1799; $C_{26}H_{24}ClN_2O$ [($M + H$) $^+$] requires m/z 379.1805.

3-[(1*H*-(5-*p*-Tolylindol)-3-yl)(4-methoxy-phenyl)methylene]-3*H*-(5-*p*-tolylindole) (12f). M.p.: 115 °C (dec); IR (KBr, ν): 3399, 1627, 1600, 1504, 1450, 1396, 1207, 1168, 1134 and 810 cm^{-1} ; 1H NMR (δ): 2.24 (s, 6H, 2 \times ArMe), 3.98 (s, 3H, 4''-OMe), 6.96 (s, 2H, 4-H and 4'-H), 7.05–7.10 (m, 4H, 6-H, 7-H, 6'-H and 7'-H), 7.29 (d, $J = 8.5$, 2H, 3''-H and 5''-H), 7.63 (d, $J = 8.5$, 2H, 2''-H and 6''-H), 7.70 (d, $J = 8.5$, 2H, 3''-H and 5''-H of *p*-tolyl), 7.88 (d, $J = 8.5$, 2H, 2''-H and 6''-H of *p*-tolyl) and 8.38 (s, 2H, 2-H and 2'-H); ^{13}C NMR (δ): 20.2, 55.9, 114.6, 114.7, 119.6, 120.8, 124.0, 126.2, 126.6, 129.1, 131.0, 136.1, 136.2, 136.4, 137.5, 138.9, 146.1, 164.3 and 166.2; EI-MS (m/z , rel. int., %): 530 (M^+ , 100), 485 (9), 439 (50), 395 (14), 257 (11), 149 (10), 97 (14) and 43 (50); HRMS found m/z 531.2420; $C_{38}H_{31}N_2O$ [($M + H$) $^+$] requires m/z 531.2431.

Typical procedure for the synthesis of oxidized tetra(indolyl)dimethanes (17)

$CeCl_3$ (0.246 g, 1.0 mmol) was added to a solution of 2,2'-bis-indole (**15**, 0, 232 g, 1.0 mmol) and the benzaldehyde derivative (**13**, 1.1 mmol) in *i*-PrOH (3 mL), and the reaction was stirred at room temperature until all the starting material was consumed (TLC). Then, water (10 mL) was added and the reaction products were extracted with EtOAc (3 \times 10 mL). The combined organic extracts were dried over $MgSO_4$, then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography (Hexanes/EtOAc, 85 : 15, v/v) to afford the corresponding product **17**.

Tetra(indolyl)dimethane derivative 18b1

IR (KBr, ν): 3406, 3051, 2920, 1681, 1604, 1508, 1450, 1338, 1211, 1168, 1010, 790 and 740 cm^{-1} ; 1H NMR (δ): 2.29 (s, 6H, 2 \times ArMe), 6.23 (s, 2H, 5-H and 10-H), 6.50 (d, $J = 8.0$, 2H), 6.57–6.61 (m, 2H), 6.67–6.75 (m, 8H), 6.95 (t, $J = 8.0$, 2H), 7.04 (d, $J = 7.6$, 4H), 7.21 (d, $J = 8.0$, 2H), 7.33 (d, $J = 8.0$, 4H), 10.31 (s, 2H, 2 \times NH) and 10.94 (s, 2H, 2 \times NH); EI-MS (m/z , rel. int., %): 668 (M^+ , 50), 577 (100), 563 (11), 448 (21), 334 (16), 288 (15) and 232 (6); HRMS found m/z 691.2808; $C_{48}H_{36}N_4Na$ [($M + Na$) $^+$] requires m/z 691.2832.

Tetra(indolyl)dimethane derivative 18b2

IR (KBr, ν): 3406, 3379, 3051, 1508, 1454, 1419, 1338, 790 and 740 cm^{-1} ; 1H NMR (δ): 2.17 (s, 6H, 2 \times ArMe), 6.48 (s, 2H, 5-H and 10-H), 6.51 (d, $J = 8.0$, 2H), 6.66 (t, $J = 7.6$, 2H), 6.77–6.84 (m, 10H), 6.92 (t, $J = 7.6$, 2H), 7.00 (d, $J = 7.6$, 2H), 7.18 (d, $J = 8.0$, 2H), 7.22 (d, $J = 7.6$, 4H), 10.66 (s, 2H, 2 \times NH) and 10.83 (s, 2H, 2 \times NH); EI-MS (m/z , rel. int., %): 668 (M^+ , 47), 577 (100), 563 (11), 448 (21), 334 (16), 288 (14) and 232 (6); HRMS found m/z 707.2572; $C_{48}H_{36}N_4K$ [($M + K$) $^+$] requires m/z 707.2567.

Oxidized tetra(indolyl)dimethane derivative 17a

M.p.: 235–238 °C (dec); IR (KBr, ν): 3421, 1612, 1577, 1512, 1446, 1338, 1249, 1176, 1033 and 748 cm^{-1} ; 1H NMR (δ): 5.52 (s, 2H, 5-H and 10-H), 6.10 (d, $J = 8.0$, 2H, 2''-H and 6'''-H),* 6.28 (d, $J = 8.0$, 2H, 7'-H), 6.58–6.64 (m, 4H, 7''-H, 3'''-H* and 5'''-H*), 6.68–6.74 (m, 4H, 5'-H and 5''-H), 6.93–7.04 (m, 8H, 6''-H, 4'''-H,* 8'''-H,* 9'''-H,* 10'''-H,* 11'''-H,* 12'''-H*), 7.13–7.20 (m, 4H, 6'-H and 4''-H), 7.58 (d, $J = 8.4$, 2H, 4'-H) and 12.40 (s, 2H, 2 \times NH); ^{13}C NMR (δ): 47.9, 68.9, 112.3, 118.8, 119.3, 120.5, 120.9, 122.2, 123.7, 123.9, 125.5, 125.6, 126.3, 126.7, 128.1, 128.6, 129.6, 129.6, 135.6, 136.2, 138.8, 156.1 and 169.8; EI-MS (m/z , rel. int., %): 638 (M^+ , 100), 561 (11), 434 (17), 344 (9), 319 (19), 231 (3) and 77 (2); HRMS found m/z 639.2546; $C_{46}H_{31}N_4$ [($M + H$) $^+$] 639.2543.

Oxidized tetra(indolyl)dimethane derivative 17b

M.p.: 241–243 °C (dec); IR (KBr, ν): 3305, 2866, 1616, 1581, 1446, 1334, 1238, 1157 and 748 cm^{-1} ; 1H NMR (δ): 2.13 (s, 6H, 2 \times ArMe), 5.49 (s, 2H, 5-H and 10-H), 5.96 (d, $J = 8.0$, 2H, 2''-H and 6'''-H),# 6.29 (d, $J = 8.0$, 2H, 7'-H), 6.43 (d, $J = 8.0$, 2H, 3'''-H and 5'''-H),* 6.61 (d, $J = 7.6$, 2H, 7''-H), 6.68–6.74 (m, 4H, 5'-H and 5''-H), 6.85 (d, $J = 7.6$, 2H, 8'''-H and 12'''-H),# 6.94–6.98 (m, 4H, 6''-H, 9'''-H* and 11'''-H*), 7.06 (d, $J = 7.6$, 2H, 4''-H), 7.19 (t, $J = 8.0$, 2H, 6'-H), 7.57 (d, $J = 8.0$, 2H, 4'-H) and 12.35 (s, 2H, 2 \times NH); ^{13}C NMR (δ): 20.3, 47.5, 69.0, 112.3, 118.8, 119.3, 120.7, 120.9, 122.2, 123.7, 123.9, 125.5, 126.4, 127.3, 128.2, 128.6, 129.4, 129.6, 132.7, 135.3, 136.3, 138.7, 156.2 and 170.0; EI-MS (m/z , rel. int., %): 666 (M^+ , 100), 575 (8), 448 (15), 333 (21) and 230 (3); HRMS found m/z 667.2842; $C_{48}H_{35}N_4$ [($M + H$) $^+$] requires m/z 667.2856.

Oxidized tetra(indolyl)dimethane derivative 17c

M.p.: 243–245 °C (dec); IR (KBr, ν): 3305, 2866, 1616, 1581, 1446, 1334, 1238, 1157 and 748 cm^{-1} ; 1H NMR (δ): 5.55 (s, 2H, 5-H and 10-H), 6.06 (d, $J = 8.4$, 2H, 2''-H and 6'''-H),# 6.32 (d, $J = 8.4$, 2H, 7'-H), 6.61 (d, $J = 7.6$, 2H, 7''-H), 6.67 (d, $J = 8.4$, 2H, 3'''-H and 5'''-H),* 6.71–6.79 (m, 4H, 5'-H and 5''-H), 6.97–7.01 (m, 4H, 6''-H, 8-H# and 12'''-H#), 7.10 (d, $J = 7.6$, 2H, 4''-H), 7.19–7.23 (m, 4H, 6'-H, 9'''-H* and 11'''-H*), 7.58 (d, $J = 8.4$, 2H, 4'-H) and 12.47 (s, 2H, 2 \times NH); ^{13}C NMR (δ): 47.2, 68.7, 112.5, 119.1, 119.5, 120.1, 120.8, 122.2, 124.0, 124.1, 125.3, 125.7, 126.7, 128.4, 128.5, 131.2 (3C), 134.7, 135.9, 138.9, 156.0 and 169.6; EI-MS (m/z , rel. int., %): 710 [($M + 2$) $^+$, 22], 708 (M^+ , 75), 706 (100), 597 (19), 468 (27), 344 (16) and 242 (6); HRMS found m/z 707.1768; $C_{46}H_{29}Cl_2N_4$ [($M + H$) $^+$] requires m/z 707.1764.

Oxidized tetra(indolyl)dimethane derivative 17d

M.p.: 237–238 °C (dec); IR (KBr, ν): 3410, 3062, 2951, 1735, 1616, 1575, 1489, 1338, 1238, 1091, 1014 and 748 cm^{-1} ; 1H NMR (δ): 3.61 (s, 6H, 2 \times ArOMe), 5.46 (s, 2H, 5-H and 10-H), 5.95 (d, $J = 8.4$, 2H, 3'''-H and 5'''-H),# 6.17 (d, $J = 8.4$, 2H, 2''-H and 6'''-H),* 6.31 (d, $J = 8.4$, 2H, 7'-H), 6.59 (d, $J = 7.6$,

2H, 7''-H), 6.68–6.76 (m, 6H, 5'-H, 5''-H, 9'''-H[#] and 11'''-H[#]), 6.88 (d, $J = 8.4$, 2H, 8'''-H and 12'''-H),* 6.96 (t, $J = 7.6$, 2H, 6''-H), 7.07 (d, $J = 7.6$, 2H, 4''-H), 7.19 (t, $J = 8.4$, 2H, 6'-H), 7.55 (d, $J = 8.4$, 2H, 4'-H) and 12.34 (s, 2H, 2 × NH); ¹³C NMR (δ): 47.1, 54.6, 69.1, 111.3, 112.0, 112.3, 118.8, 119.3, 120.9, 120.9, 122.1, 123.6, 123.8, 125.5, 127.7, 128.1, 128.5, 130.4, 130.7, 136.4, 138.7, 156.2, 157.6 and 170.0; EI-MS (m/z , rel. int., %): 699 (M⁺, 57), 698 (100), 593 (52), (49), 349 (24), 232 (6) and 77 (8); HRMS found m/z 699.2753; C₄₈H₃₅N₄O₂ [(M + H)⁺] requires m/z 699.2754.

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