



ortho-Carbaborane derivatives of indomethacin as cyclooxygenase (COX)-2 selective inhibitors

Matthias Scholz^a, Anna L. Blobaum^b, Lawrence J. Marnett^{b,c,d,e}, Evamarie Hey-Hawkins^{a,*}

^a Institut für Anorganische Chemie der Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany

^b A. B. Hancock Jr. Memorial Laboratory for Cancer Research, Department of Biochemistry, Vanderbilt Institute for Chemical Biology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

^c A. B. Hancock Jr. Memorial Laboratory for Cancer Research, Department of Chemistry, Vanderbilt Institute for Chemical Biology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

^d A. B. Hancock Jr. Memorial Laboratory for Cancer Research, Department of Pharmacology, Vanderbilt Institute for Chemical Biology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

^e Center in Molecular Toxicology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37232, USA

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ABSTRACT

A series of novel indomethacin analogues with carbaboranes as three-dimensional substitutes for the chlorophenyl ring have been prepared. Their cyclooxygenase (COX) inhibition and enzyme selectivity has been tested and compared to the corresponding adamantyl analogues. Surprisingly, only the *ortho*-carbaborane derivatives were active compounds. Preliminary biological studies gave an interesting insight into the validity of employing carbaboranes as pharmacophores.

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1. Introduction

Indomethacin 2-[1-(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl]acetic acid is an indole-based nonsteroidal anti-inflammatory drug (NSAID). It is administered as an analgesic and anti-inflammatory agent to treat fever, edema and pain.^{1,2} Indomethacin's therapeutic effects arise from the inhibition of cyclooxygenase (COX) enzymes and blockade of prostaglandin synthesis.^{3,4} COX exists as two different isoforms, COX-1 and COX-2. COX-1 is the so-called 'housekeeping' enzyme, because it is constitutively expressed, whereas COX-2 is highly inducible at sites of inflammation.^{5–9} COX-2 expression is highly elevated in cancer cells.¹⁰ Therefore, the COX-2 variant emerged as favored drug target.¹¹ Classical NSAIDs, such as indomethacin (IC₅₀ values of 0.05 μM for COX-1 and 0.75 μM for COX-2), inhibit both enzyme variants.¹² Since the active site of COX-2 is approximately 25% larger than that of COX-1, a size-extension of classical NSAIDs successfully yielded inhibitors with COX-2 selectivity.^{13–15} Indomethacin offers two possible positions in the periphery of the indole core for the introduction of bulky substituents in order to induce the desired selectivity (Fig. 1).^{16–19}

* Corresponding author.

E-mail address: hey@rz.uni-leipzig.de (E. Hey-Hawkins).

The carboxylic acid functional group allows for various changes, which have already extensively been studied.^{12,20} Transformations of the chlorophenyl ring are synthetically more challenging, but revealed also very potent inhibitors.^{16,21} The presence of two additional chlorine substituents *meta* to the already present chlorine atom at the *para* position created a highly selective COX-2 inhibitor.¹⁶ The chlorine residues increased both size and electron deficiency of the benzoyl group. These two effects are probably responsible for the introduction of COX-2 selectivity.

The common modifications at the phenyl ring, however, allow only for a two-dimensional extension of the disc-shaped structure. To increase the volume three-dimensionally, different spherical substituents are required. Therefore, we selected the organic adamantyl moiety and the inorganic dicarba-*closo*-dodecaborane(12) (carbaborane) clusters. The latter seemed very promising, because they combine both bulkiness and electron deficiency.^{22,23}

Carbaboranes are icosahedral clusters of ten BH units and two CH vertices with the latter organized either in *ortho* (*o*), *meta* (*m*), or *para* fashion (*p*, Scheme 1).^{24–26} The clusters occupy a volume similar to adamantane and are a little larger than a rotating benzene ring. Because of the delocalization of the cluster electrons, carbaboranes are also described as three-dimensional benzene analogues. The size of the carbaborane isomers is virtually the same, their intrinsic electronic properties, however, differ. Most

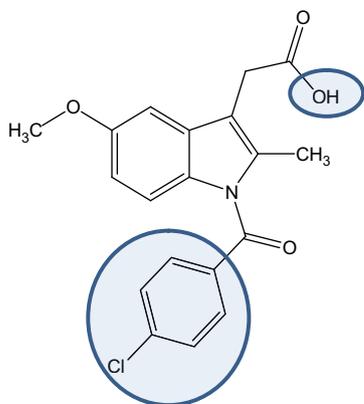


Figure 1. Indomethacin with two possible modification sites (highlighted) to obtain COX-2 selectivity.

characteristically is the electron-withdrawing effect which decreases in the order *ortho*- to *para*-carbaborane.^{27,28} The aim of this study was therefore to synthesize all three cluster analogues of indomethacin and to determine whether carbaboranes can be used as surrogates for the chlorophenyl ring to induce COX-2 selectivity.

2. Results

2.1. Chemistry

The carbaborane analogues of indomethacin (**4o–p**) could successfully be prepared in very good overall yields (Scheme 1).

The most challenging step was the choice of a proper protecting ester group, which should easily be introduced and later easily removed. Firstly, the methyl ester **1** was chosen, because it is already available.²⁰ Transformation into the carbaborane analogues **1o–p** afterwards was also successful, but surprisingly, deprotection later on failed completely. Thus, thiols,²⁹ BBr₃,³⁰ Me₃SnOH^{31,32} and different lipases³³ were either inactive, cleaved preferably the methoxy ether group or eliminated the carbaborane substituent. Thus, the benzyl (**2**) and *tert*-butyl (**3**) esters were prepared, because of different deprotection protocols (Scheme 1).

The benzyl ester could be obtained via *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) activation in analogy to **1**.³⁴ Reduction of the amount of alcohol from four to 1 equiv was found to be sufficient and even crucial to facilitate purification (separation from unreacted benzyl alcohol). The use of BOP-Cl failed to provide **3** in good yield (<20%). The same was observed when adamantanol was used. The nucleophilic attack of tertiary alcohols at the BOP-coupled and thus activated acid is probably sterically too hindered to guarantee high conversions in the presence of the free secondary indole nitrogen group. An alternative strategy, use of *tert*-butyl acetoacetate in combination with catalytic amounts of different acids, also failed, as well as the classic *N,N'*-diisopropylcarbodiimide (DIC) activation method.³⁵ However, with CuCl and *tert*-butanol, DIC was transformed into 2-*tert*-butyl-1,3-diisopropylisourea (active *tert*-Bu), which finally produced the ester in satisfying yield (Scheme 1).³⁶

A convenient method to introduce the carbaborane substituent at the indole nitrogen is salt elimination. The carbaboranyl chlorides were obtained from the unsubstituted clusters in excellent yields by slightly modified literature procedures via the corresponding carboxylic acids.³⁷ A screening of different bases revealed NaN(SiMe₃)₂ as the base of choice. NaN(SiMe₃)₂ was better than NaH and superior to different lithium bases tested. Abandonment of aqueous workup after the reaction additionally increased the yields.

The methyl ester could not selectively be deprotected, cleavage of the benzyl and *tert*-butyl ester, however, gave the target compounds in excellent yields. The *tert*-butyl group could easily be removed using trifluoroacetic acid (TFA), the benzyl group could reductively be eliminated with Pd/H₂.³⁸ In the case of the carbaboranyl analogues, the *tert*-butyl strategy is preferred. It is easy to perform and did not harm the amide bond, which was partly cleaved under reducing conditions in the case of the *ortho* isomer. To deprotect the adamantyl-substituted analogue, the benzyl strategy is required, because TFA also eliminates the adamantyl substituent.

All carbaboranyl analogues (**4o, m, p**) were isolated as solids and recrystallized for X-ray structure determination (Fig. 2).

As esterification of the carboxylic acid in indomethacin induces COX-2 selectivity, the esters (**1o–3p**) represent also potential drug candidates. To study the impact of the cluster in place of the chlorophenyl ring, COX inhibition of these esters was also tested and compared to the corresponding indomethacin esters (OH in Fig. 1 replaced by OMe (**1i**, 84%), OBn (**2i**, 88%) or O(*tert*-Bu) (**3i**, 56% yield). The latter were synthesized using BOP-Cl for activation of the carboxylic acid.³⁹

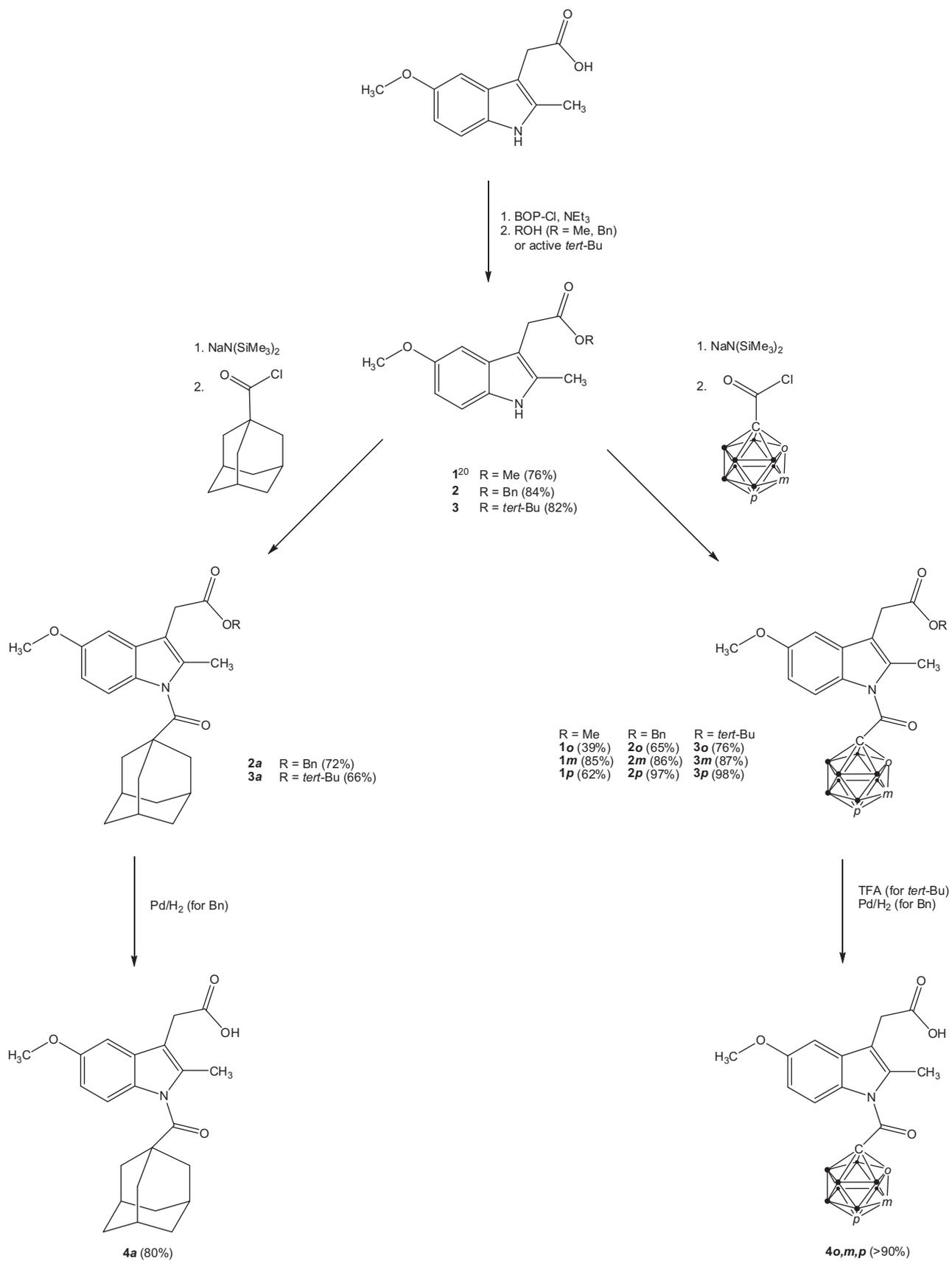
2.2. COX-inhibition studies

To select the most promising drug candidates for COX inhibition, all compounds were initially screened at 25 μM concentration in a radioactivity assay measuring the conversion of [¹⁴C]-arachidonic acid (AA) to [¹⁴C]-prostaglandins. The assay monitors the change in [¹⁴C]-AA in the absence/presence of inhibitor relative to a control. Surprisingly, only the *ortho*-carbaborane derivatives (**o** series) revealed highly active compounds, whereas all compounds containing *meta*-, *para*-carbaboranyl and adamantyl substituents (**m, p, and a** series) were inactive (Table 1).

The *ortho* (**o**) series additionally revealed the desired selectivity shift in favor of COX-2. The *ortho*-carbaborane analogue of indomethacin 1-(1-carboxy-1,2-dicarba-*closo*-dodecaboran(12)yl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid (**4o**) (indoborin), inhibited COX-2 in the low micromolar range (IC_{50(COX-2)} = 3.68 μM) and was inactive against COX-1 at concentrations lower than 25 μM. Surprisingly, methyl ester **1o**, which proved difficult to be deprotected, was the best COX-2 inhibitor acting in the nanomolar range (IC_{50(COX-2)} = 84 nM) while inhibiting COX-1 in only micromolar concentrations (IC_{50(COX-1)} = 12.8 μM).

Hence, *ortho*-carbaborane emerged as magnificent surrogate for the chlorophenyl ring of indomethacin to induce COX-2 selectivity in contrast to the other bulky substituents, such as *meta*-, *para*-carbaborane and adamantyl. As all carbaboranes differ only negligibly in their volumes, the unique electronic properties of *ortho*-carbaborane seem to be the reason for inducing both COX inhibition in general and in particular COX-2 selectivity. The presence of an additional ester group in the *ortho*-carbaboranyl analogues could further fine-tune the COX selectivity profile. The best COX-2 inhibitor tested was **1o** with the small methyl ester group. Compound **1o** and the aromatic benzyl ester **2o** also inhibited COX-1, but in the case of **1o** the IC₅₀ value was three orders of magnitude lower for COX-2. The bulky *tert*-butyl ester **3o** and the free acid **4o** exclusively inhibited COX-2 and not COX-1 in the relevant concentration range. All esters of the **o** series were better inhibitors than the corresponding indomethacin esters with the chlorophenyl substituent.

We had previously investigated carbaboranyl esters of indomethacin. This approach only succeeded to lower COX-1 inhibition, but failed to induce a clear COX-2 selectivity. Interestingly, these studies also showed *ortho*-carbaborane directly attached to the carboxylate group as the only active inhibitor.⁴⁰



Scheme 1. Synthesis of the modified indomethacin analogues (● = BH, *o*-, *m*-, *p* = *o*, *m*, or *p*-CH).

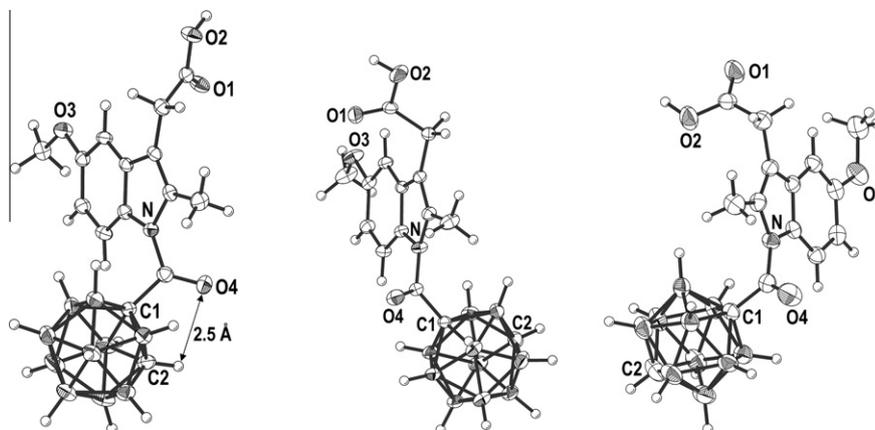


Figure 2. ORTEP of **4o**, **m**, **p** with selected atoms labeled, thermal ellipsoids are drawn at 50% probability. Compound **4p** crystallized with disordered *n*-pentane, **4o** and **4m** crystallized solvent-free.

Table 1

IC₅₀ values as determined in a radioactivity assay

Compound	IC ₅₀ (μM)	
	COX-1	COX-2
Indomethacin	0.027	0.127
Indomethacin methyl ester (11) ³⁹	>25	0.250
Indoborin (4o)	>25	3.680
Indoborin methyl ester (1o)	12.800	0.084
Indoborin benzyl ester (2o)	15.050	11.600
Indoborin <i>tert</i> -butyl ester (3o)	>25	1.410

All other compounds (*meta*-, *para*-, adamantyl series, benzyl and *tert*-butyl ester of indomethacin) were inactive in concentrations as high as 25 μM. Data are representative of an average of at least two independent experiments.

3. Summary and conclusion

In conclusion, carbaboranes are unique and yet underrepresented pharmacophores.^{23d} Their versatile chemistry allows the integration of the clusters into various drug candidates in high-yielding procedures. The results of the indomethacin derivatives indicate that the syntheses of all cluster analogues are rather similar, whereas the resulting biochemical profile clearly depends on the carbaborane isomer. The COX inhibition potential of *meta*- and *para*-carbaborane was similar to the adamantyl analogue, which can therefore be regarded as being determined by geometric features only. The pronounced activity of the strong electron-withdrawing *ortho*-carbaborane derivatives, however, suggests that this isomer acts via its functionality. A detailed investigation (co-crystallization of **1o–4o** with COX-2 and corresponding modeling studies) to understand the unexpected activity of the *ortho*-carbaborane derivatives is currently underway.

4. Experimental

4.1. Chemistry

4.1.1. General

All reactions were carried out under nitrogen atmosphere by using standard Schlenk techniques. The solvents were purified by a Solvent Purification System SPS-800 Series. All alcohols were distilled prior usage. Carbaboranes are commercially available from Katchem (Czech Republic). 5-Methoxy-2-methyl-1*H*-indole-3-acetic acid is commercially available (a facile synthesis is given in the Supplementary data). 5-Methoxy-2-methyl-1*H*-indole-3-acetic acid methyl ester (**1**) was prepared according to the literature.²⁰

Flash chromatography was carried out on Merck SilicaGel 60 (0.035–0.070 mm). Merck Silica 60 F254 was used for thin-layer chromatography (TLC). The TLC plates were developed with palladium(II) chloride methanol solution. The infrared spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrometer as KBr pellets. The ¹H, ¹³C, and ¹¹B NMR spectra were recorded at 25 °C on an AVANCE DRX 400 spectrometer (Bruker). The chemical shifts for the ¹H, ¹³C, and ¹¹B NMR spectra are reported in parts per million (ppm) at 400.13, 100.63, and 128.38 MHz, respectively, with tetramethylsilane as standard for the first two and BF₃(OEt₂) as external standard for ¹¹B NMR. Proton-coupled ¹³C NMR spectra were not recorded for carbaborane-containing compounds; ²J_{CH} were not always resolved. The number of boron atoms and ¹J_{BH} could not always be determined unambiguously due to broad and overlapping signals. Elemental analyses were recorded on a VARIO EL (Heraeus). The melting points were determined in capillaries (GALLENKAMP) and represent uncorrected values. The crystals for crystal structure determination were obtained from concentrated solutions at room temperature. The crystallographic data were collected on a CCD Oxford Xcalibur S diffractometer (λ(Mo-Kα) = 0.71073 Å) in ω and ϕ scan mode. Semi-empirical from equivalents absorption corrections were carried out with SCALE3 ABSPACK and the structures were solved with direct methods.^{41,42} Structure refinement was carried out with SHELXL-97.⁴³ CCDC 808548–808550 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

4.1.2. Syntheses

4.1.2.1. Esters of 5-methoxy-2-methyl-1*H*-indole-3-acetic acid.
4.1.2.1.1. 5-Methoxy-2-methyl-1*H*-indole-3-acetic acid benzyl ester (2**).** 5-Methoxy-2-methyl-1*H*-indole-3-acetic acid (4.00 g, 18.26 mmol) and BOP-Cl (4.65 g, 18.26 mmol) were suspended in dichloromethane (1 mL) and NEt₃ (5.0 mL, 35.90 mmol) was slowly added and the mixture stirred for 10 min. Benzyl alcohol (1.9 mL, 18.26 mmol) was added and the mixture stirred for 12 h. Dichloromethane (200 mL) was added and the reaction mixture was washed with water (2 × 200 mL) and brine solution (100 mL). The organic layer was concentrated and purified by column chromatography with a mixture of hexanes (80–100 °C) and ethyl acetate (2:1) for elution. The solvent was removed under reduced pressure to yield the corresponding ester as yellow solid. Yield: 4.74 g (84%); elemental Anal. Calcd for C₁₉H₁₉NO₃: C, 73.77; H, 6.19. Found: C, 73.13; H, 6.19; mp: 55–56 °C; ESI MS (+) (CH₃OH/CHCl₃): *m/z*: 326.1 (100%, [M+OH]⁺); ¹H NMR (CDCl₃, ppm): 7.75

(s, br, 1H, NH_{indole}), 7.29–7.23 (vbr, 5H, CH_{phenyl}, together with solvent residual peak), 7.06 (d, ³J_{HH} = 8 Hz, 1H, CH_{indole}), 6.96 (d, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 6.75 (dd, ³J_{HH} = 8 Hz, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 5.10 (s, 2H, CH₂ benzyl), 3.76 (s, 3H, OCH₃), 3.69 (s, 2H, CH₂), 2.29 (s, 3H, CH₃); ¹³C{¹H} NMR (CDCl₃, ppm): 172.0 (COO), 154.0 (C_{indole}O), 136.0 (C_{aromat}), 133.7 (C_{aromat}), 130.1 (C_{aromat}), 128.8 (C_{aromat}), 128.5 (CH_{phenyl}), 128.1 (C_{aromat}H), 128.0 (CH_{phenyl}), 111.0 (C_{aromat}H), 111.0 (C_{aromat}H), 104.1 (C_{aromat}H), 100.2 (C_{aromat}H), 66.5 (CH₂ benzyl), 55.8 (OCH₃), 30.5 (CH₂), 11.7 (CH₃); IR (selected, KBr, cm⁻¹): $\tilde{\nu}$ = 3400 (s, ν (N–H)), 3033 (w), 2938 (w), 1729 (s, ν (C=O)).

4.1.2.1.2. 5-Methoxy-2-methyl-1H-indole-3-acetic acid tert-butyl ester (3). DIC (12.1 mL, 77.8 mmol) was added to a mixture of CuCl (140 mg, 1.4 mmol) and *tert*-butanol (29.9 mL, 312.6 mmol) and the mixture was stirred at room temperature for 12 h. The volatile components were removed under reduced pressure. The solid was dissolved in THF (25 mL) and 5-methoxy-2-methyl-1H-indole-3-acetic acid (**2**) (7.0 g, 31.9 mmol) was added and the mixture stirred at room temperature for 2 h. The solvent was evaporated and the solid was purified by column chromatography with a mixture of hexanes (80–100 °C) and ethyl acetate (3:1). The solvent was removed under reduced pressure to yield a white solid. Yield: 7.2 g (82%); elemental Anal. Calcd for C₁₆H₂₁NO₃: C, 69.80; H, 7.69. Found: C, 69.57; H, 7.67; mp: 110–111 °C; ESI MS (–) (CH₃COCH₃): *m/z*: 274.0 (100%, [M–H][–]); ¹H NMR (CDCl₃, ppm): 7.75 (s, vbr, NH_{indole}), 7.14 (d, ³J_{HH} = 8 Hz, 1H, CH_{indole}), 7.00 (d, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 6.76 (dd, ³J_{HH} = 8 Hz, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 3.85 (s, 3H, OCH₃), 3.54 (s, 2H, CH₂), 2.39 (s, 3H, CH₃), 1.43 (s, 9H, C(CH₃)₃); ¹³C{¹H} NMR (CDCl₃, ppm): 171.4 (COO), 154.0 (C_{indole}O), 133.5 (C_{indole}), 130.2 (C_{indole}), 129.1 (C_{indole}), 110.9 (C_{indole}H), 110.9 (C_{indole}H), 105.0 (C_{indole}), 100.6 (C_{indole}H), 80.5 (C(CH₃)₃), 55.9 (OCH₃), 31.9 (CH₂), 28.1 (C(CH₃)₃), 11.9 (CH₃); IR (selected, KBr, cm⁻¹): $\tilde{\nu}$ = 3342 (s, ν (N–H)), 3005 (w), 2980 (w), 2965 (w), 2914 (w), 2837 (w), 2047 (w), 1722 (s, ν (C=O)).

4.1.2.2. Substitutions at the indole NH group. **4.1.2.2.1. General procedure.** NaN(SiMe₃)₂ (1.1 equiv, in toluene) was added at –78 °C to the ester (1 equiv) dissolved in toluene (1.5 mL/100 mg) and the mixture was stirred for 1 h at room temperature. The corresponding carbaboranyl carbonyl chloride (1.3 equiv, stock solution in toluene) was added and the mixture stirred additionally for 12 h. The solvent was evaporated and the solid was purified by column chromatography with a mixture of hexanes (80–100 °C) and ethyl acetate (3:1). The solvent was removed under reduced pressure to yield the corresponding esters as slightly yellow solids.

4.1.2.2.2. 1-(1-Carboxy-1,2-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid methyl ester (10). Yield: 0.10 g (39% from 0.15 g **1**); elemental Anal. Calcd for C₁₆H₂₅B₁₀NO₄: C, 47.64; H, 6.25. Found: C, 47.98; H, 6.31; ESI MS (+) (CH₃COCH₃): *m/z*: 442.1 (100%, [M+K]⁺), 404.3 (75%, [M+H]⁺); mp: 126–127 °C, ¹H NMR (CDCl₃, ppm): 7.32 (d, ³J_{HH} = 8 Hz, 1H, CH_{indole}), 6.95 (d, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 6.85 (dd, ³J_{HH} = 8 Hz, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 4.36 (s, 1H, C_{cluster}H), 3.86 (s, 3H, OCH₃), 3.69 (s, 3H, COOCH₃), 3.63 (s, 2H, CH₂), 3.30–1.40 (m, vbr, 10H, C₂H₁₀B₁₀), 2.31 (s, 3H, CH₃); ¹¹B NMR (CDCl₃, ppm): –1.3 (d, ¹J_{BH} = 154 Hz, C₂H₁₀B₁₀), –2.5 (d, ¹J_{BH} = 141 Hz, C₂H₁₀B₁₀), –8.5 (d, ¹J_{BH} = 192 Hz, C₂H₁₀B₁₀), –12.0 (vbr, C₂H₁₀B₁₀), –13.1 (vbr, C₂H₁₀B₁₀); ¹³C NMR (CDCl₃, ppm): 171.1 (s, CO), 166.6 (s, CO), 156.0 (s, C_{indole}O), 135.1 (m, vbr, C_{indole}), 130.1 (m, vbr, C_{indole}), 130.0 (m, vbr, C_{indole}), 113.2 (d, ¹J_{CH} = 161 Hz, C_{indole}H), 112.0 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 111.3 (C_{indole}), 101.5 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 74.6 (vbr, C_{cluster}), 59.2 (d, vbr, ¹J_{CH} = 201 Hz, C_{cluster}H), 55.8 (q, ¹J_{CH} = 141 Hz, OCH₃), 52.2 (q, ¹J_{CH} = 141 Hz, OCH₃), 30.2 (t, ¹J_{CH} = 131 Hz, CH₂), 11.4 (q, ¹J_{CH} = 131 Hz, CH₃); IR (selected, KBr, cm⁻¹): $\tilde{\nu}$ = 3055 (w), 2955 (w), 2918 (w), 2602 (s, ν (B–H)), 2580 (s, ν (B–H)), 1743 (s, ν (C=O)), 1712 (s, ν (C=O)).

4.1.2.2.3. 1-(1-Carboxy-1,7-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid methyl ester (1m). Yield: 1.06 g (85% from 0.72 g **1**); elemental Anal. Calcd for C₁₆H₂₅B₁₀NO₄: C, 47.64; H, 6.25. Found: C, 47.35; H, 6.21; mp: 103–104 °C; ESI MS (+) (CH₃COCH₃): *m/z*: 442.1 (48%, [M+K]⁺), 404.2 (100%, [M+H]⁺); ¹H NMR (CDCl₃, ppm): 7.25 (d, ³J_{HH} = 8 Hz, 1H, CH_{indole}), 6.93 (d, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 6.82 (dd, ³J_{HH} = 8 Hz, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 3.85 (s, 3H, OCH₃), 3.68 (s, 3H, COOCH₃), 3.62 (s, 2H, CH₂), 3.06 (s, 1H, C_{cluster}H), 3.30–1.40 (m, vbr, 10H, C₂H₁₀B₁₀), 2.27 (s, 3H, CH₃); ¹¹B NMR (CDCl₃, ppm): –4.7 (d, ¹J_{BH} = 154 Hz, 1B, C₂H₁₀B₁₀), –5.8 (d, ¹J_{BH} = 128 Hz, 1B, C₂H₁₀B₁₀), –10.4 (d, ¹J_{BH} = 141 Hz, 4B, C₂H₁₀B₁₀), –13.1 (d, ¹J_{BH} = 169 Hz, 2B, C₂H₁₀B₁₀), –15.2 (d, ¹J_{BH} = 192 Hz, 2B, C₂H₁₀B₁₀); ¹³C NMR (CDCl₃, ppm): 171.3 (m, vbr, CO), 167.3 (s, CO), 155.5 (m, vbr, C_{indole}O), 134.9 (q, ²J_{CH} = 6 Hz, C_{indole}CH₃), 130.4 (t, ²J_{CH} = 10 Hz, C_{indole}), 129.5 (m, vbr, C_{indole}), 112.8 (d, ¹J_{CH} = 161 Hz, C_{indole}H), 111.8 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 109.9 (m, vbr, C_{indole}), 101.1 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 78.1 (vbr, C_{cluster}), 55.8 (q, ¹J_{CH} = 141 Hz, OCH₃), 55.0 (d, vbr, ¹J_{CH} = 181 Hz, C_{cluster}H), 52.1 (q, ¹J_{CH} = 141 Hz, OCH₃), 30.2 (t, ¹J_{CH} = 131 Hz, CH₂), 11.3 (q, ¹J_{CH} = 131 Hz, CH₃); IR (selected, KBr, cm⁻¹): $\tilde{\nu}$ = 3047 (s, ν (C–H)), 3025 (w), 2953 (s, ν (C–H)), 2903 (w), 2836 (w), 2663 (m, ν (B–H)), 2611 (s, ν (B–H)), 1728 (s, ν (C=O)).

4.1.2.2.4. 1-(1-Carboxy-1,12-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid methyl ester (1p). Yield: 0.16 g (62% from 0.15 g **1**); elemental Anal. Calcd for C₁₆H₂₅B₁₀NO₄: C, 47.64; H, 6.25. Found: C, 47.83; H, 6.19; mp: 115–116 °C; ESI MS (+) (CH₃COCH₃): *m/z*: 442.1 (34%, [M+K]⁺), 404.2 (100%, [M+H]⁺); ¹H NMR (CDCl₃, ppm): 7.13 (d, ³J_{HH} = 8 Hz, 1H, CH_{indole}), 6.91 (d, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 6.80 (dd, ³J_{HH} = 8 Hz, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 3.84 (s, 3H, OCH₃), 3.67 (s, 3H, COOCH₃), 3.59 (s, 2H, CH₂), 3.50–1.50 (m, vbr, 10H, C₂H₁₀B₁₀), 2.91 (s, 1H, C_{cluster}H), 2.18 (s, 3H, CH₃); ¹¹B NMR (CDCl₃, ppm): –13.0 (d, ¹J_{BH} = 180 Hz, 5B, C₂H₁₀B₁₀), –15.1 (d, ¹J_{BH} = 167 Hz, 5B, C₂H₁₀B₁₀); ¹³C NMR (CDCl₃, ppm): 171.4 (m, vbr, CO), 168.0 (s, CO), 155.4 (m, vbr, C_{indole}O), 134.8 (m, vbr, C_{indole}), 130.5 (m, vbr, C_{indole}), 129.2 (m, vbr, C_{indole}), 112.7 (d, ¹J_{CH} = 161 Hz, C_{indole}H), 111.7 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 109.4 (m, vbr, C_{indole}), 101.0 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 85.3 (vbr, C_{cluster}), 63.8 (d, vbr, ¹J_{CH} = 181 Hz, C_{cluster}H), 55.8 (q, ¹J_{CH} = 141 Hz, OCH₃), 52.1 (q, ¹J_{CH} = 141 Hz, OCH₃), 30.2 (t, ¹J_{CH} = 131 Hz, CH₂), 11.1 (q, ¹J_{CH} = 131 Hz, CH₃); IR (selected, KBr, cm⁻¹): $\tilde{\nu}$ = 3047 (s, ν (C–H)), 2997 (w), 2950 (w), 2605 (s, ν (B–H)), 1729 (s, ν (C=O)).

4.1.2.2.5. 1-(1-Carboxy-1,2-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid benzyl ester (20). Yield: 0.20 g (65% from 0.20 g **2**); elemental Anal. Calcd for C₂₂H₂₉B₁₀NO₄: C, 55.10; H, 6.09. Found: C, 55.15; H, 6.11; mp: 53–54 °C; ESI MS (–) (CH₃COCH₃): *m/z*: 375.3 (100%, [M–CH₃–CH₂C₆H₅][–]); ¹H NMR (CDCl₃, ppm): 7.38–7.26 (m, vbr, 6H, CH_{aromat} together with solvent residual peak), 6.92 (d, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 6.85 (dd, ³J_{HH} = 8 Hz, ⁴J_{HH} = 2 Hz, 1H, CH_{indole}), 5.11 (s, 2H, CH₂ benzyl), 4.36 (s, 1H, C_{cluster}H), 3.78 (s, 3H, OCH₃), 3.67 (s, 2H, CH₂), 3.36–1.49 (m, vbr, 10H, C₂H₁₀B₁₀), 2.29 (s, 3H, CH₃); ¹¹B NMR (CDCl₃, ppm): –1.2 (d, ¹J_{BH} = 128 Hz, 1B, C₂H₁₀B₁₀), –2.5 (d, ¹J_{BH} = 154 Hz, 1B, C₂H₁₀B₁₀), –8.5 (d, ¹J_{BH} = 154 Hz, 2B, C₂H₁₀B₁₀), –11.9 (vbr, 3B, C₂H₁₀B₁₀), –13.0 (vbr, 3B, C₂H₁₀B₁₀); ¹³C NMR (CDCl₃, ppm): 170.4 (s, vbr, CO), 166.6 (s, vbr, CO), 156.0 (s, vbr, C_{indole}O), 135.6 (s, vbr, C_{aromat}), 135.1 (s, vbr, C_{aromat}), 130.1 (s, vbr, C_{aromat}), 130.0 (s, vbr, C_{aromat}), 128.6 (m, vbr, CH_{phenyl}), 128.3 (m, vbr, CH_{phenyl}), 128.1 (m, vbr, CH_{phenyl}), 113.2 (d, ¹J_{CH} = 161 Hz, C_{indole}H), 112.3 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 111.2 (s, vbr, C_{aromat}), 101.4 (dd, ¹J_{CH} = 161 Hz, ²J_{CH} = 5 Hz, C_{indole}H), 74.6 (s, vbr, C_{cluster}), 66.8 (tt, ¹J_{CH} = 151 Hz, ²J_{CH} = 4 Hz, OCH₂), 59.2 (d, ¹J_{CH} = 201 Hz, C_{cluster}H), 55.7 (q, ¹J_{CH} = 141 Hz, OCH₃), 30.5 (t, ¹J_{CH} = 131 Hz, CH₂), 11.4 (q, ¹J_{CH} = 131 Hz, CH₃); IR (selected, KBr, cm⁻¹): $\tilde{\nu}$ = 3431 (w), 3064 (w), 2928 (w), 2834 (w), 2586 (m, ν (B–H)),

1733 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.6. 1-(1-Carboxy-1,7-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid benzyl ester (**2m**). Yield: 0.53 g (86% from 0.40 g **2**); elemental Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{B}_{10}\text{NO}_4$: C, 55.10; H, 6.09. Found: C, 54.70; H, 6.13; mp: 57–58 °C; ESI MS (+) ($\text{CH}_3\text{COCH}_3/\text{CHCl}_3/\text{Na}^+$): m/z : 537.1 (100%, $[\text{M}+\text{CH}_3\text{COCH}_3]^+$); ^1H NMR (CDCl_3 , ppm): 7.31–7.26 (vbr, 6H, $\text{CH}_{\text{aromat}}$ together with solvent residual peak), 6.91 (s, 1H, $\text{CH}_{\text{aromat}}$), 6.82 (d, $^1J_{\text{HH}} = 8$ Hz, 1H, $\text{CH}_{\text{aromat}}$), 5.11 (s, 2H, CH_2 benzyl), 3.77 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2), 3.05 (s, 1H, $\text{C}_{\text{clusterH}}$), 3.50–1.50 (m, vbr, 10H, $\text{C}_2\text{H}_{10}\text{B}_{10}$), 2.26 (s, 3H, CH_3); ^{11}B NMR (CDCl_3 , ppm): –4.8 (vbr, 1B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –5.8 (vbr, 1B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –10.5 (d, $^1J_{\text{BH}} = 154$ Hz, 4B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –13.1 (d, $^1J_{\text{BH}} = 180$ Hz, 2B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –15.3 (vbr, 2B, $\text{C}_2\text{H}_{10}\text{B}_{10}$); ^{13}C NMR (CDCl_3 , ppm): 170.7 (s, vbr, CO), 167.3 (s, CO), 155.5 (s, vbr, $\text{C}_{\text{indoleO}}$), 135.7 (s, C_{aromat}), 134.9 (s, C_{aromat}), 130.4 (s, vbr, C_{aromat}), 129.4 (s, vbr, C_{aromat}), 128.5 (m, vbr, $\text{CH}_{\text{phenyl}}$), 128.2 (m, vbr, $\text{CH}_{\text{phenyl}}$), 128.0 (m, vbr, $\text{CH}_{\text{phenyl}}$), 112.8 (d, $^1J_{\text{CH}} = 161$ Hz, $\text{C}_{\text{indoleH}}$), 112.0 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 5$ Hz, $\text{C}_{\text{indoleH}}$), 109.8 (s, vbr, C_{aromat}), 101.0 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 5$ Hz, $\text{C}_{\text{indoleH}}$), 78.1 (s, $\text{C}_{\text{cluster}}$), 66.7 (t, $^1J_{\text{CH}} = 151$ Hz, OCH_2), 55.7 (q, $^1J_{\text{CH}} = 141$ Hz, OCH_3), 55.0 (d, $^1J_{\text{CH}} = 181$ Hz, $\text{C}_{\text{clusterH}}$), 30.5 (t, $^1J_{\text{CH}} = 131$ Hz, CH_2), 11.3 (q, $^1J_{\text{CH}} = 131$ Hz, CH_3); IR (selected, KBr, cm^{-1}): $\tilde{\nu} = 3061$ (w), 2996 (w), 2925 (w), 2834 (w), 2609 (s, $\nu(\text{B-H})$), 1733 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.7. 1-(1-Carboxy-1,12-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid benzyl ester (**2p**). Yield: 0.30 g (97% from 0.20 g **2**); elemental Anal. Calcd for $\text{C}_{22}\text{H}_{29}\text{B}_{10}\text{NO}_4$: C, 55.10; H, 6.09. Found: C, 54.70; H, 6.13; mp: 77–78 °C; ESI MS (+) (CH_3COCH_3): m/z : 537.3 (100%, $[\text{M}+\text{CH}_3\text{COCH}_3]^+$); ^1H NMR (CDCl_3 , ppm): 7.31–7.26 (vbr, 5H, $\text{CH}_{\text{phenyl}}$ together with solvent residual peak), 7.13 (d, 1H, $^3J_{\text{CH}} = 8$ Hz, $\text{CH}_{\text{indole}}$), 6.88 (d, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.79 (dd, 1H, $^3J_{\text{CH}} = 8$ Hz, $^4J_{\text{HH}} = 2$ Hz, $\text{CH}_{\text{indole}}$), 5.11 (s, 2H, CH_2 benzyl), 3.76 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2), 3.33–1.49 (m, vbr, 10H, $\text{C}_2\text{H}_{10}\text{B}_{10}$), 2.90 (s, 1H, $\text{C}_{\text{clusterH}}$), 2.16 (s, 3H, CH_3); ^{11}B NMR (CDCl_3 , ppm): –13.0 (d, $^1J_{\text{BH}} = 154$ Hz, 5B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –15.1 (d, $^1J_{\text{BH}} = 167$ Hz, 5B, $\text{C}_2\text{H}_{10}\text{B}_{10}$); ^{13}C NMR (CDCl_3 , ppm): 170.7 (s, vbr, CO), 167.9 (s, CO), 155.3 (s, vbr, $\text{C}_{\text{indoleO}}$), 135.8 (s, vbr, C_{aromat}), 134.8 (s, vbr, C_{aromat}), 130.5 (s, vbr, C_{aromat}), 129.1 (s, vbr, C_{aromat}), 128.5 (s, vbr, $\text{CH}_{\text{phenyl}}$), 128.2 (s, vbr, $\text{CH}_{\text{phenyl}}$), 128.0 (s, vbr, $\text{CH}_{\text{phenyl}}$), 112.7 (d, $^1J_{\text{CH}} = 161$ Hz, $\text{C}_{\text{indoleH}}$), 111.9 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 5$ Hz, $\text{C}_{\text{indoleH}}$), 109.3 (s, vbr, C_{indole}), 100.8 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 5$ Hz, $\text{C}_{\text{indoleH}}$), 85.3 (s, vbr, $\text{C}_{\text{cluster}}$), 66.6 (tt, $^1J_{\text{CH}} = 141$ Hz, $^3J_{\text{CH}} = 5$ Hz, OCH_2), 63.8 (d, $^1J_{\text{CH}} = 181$ Hz, $\text{CH}_{\text{cluster}}$), 55.7 (q, $^1J_{\text{CH}} = 141$ Hz, OCH_3), 30.5 (t, $^1J_{\text{CH}} = 131$ Hz, CH_2), 11.2 (q, $^1J_{\text{CH}} = 131$ Hz, CH_3); IR (selected, KBr, cm^{-1}): $\tilde{\nu} = 3060$ (w), 2929 (w), 2617 (s, $\nu(\text{B-H})$), 1727 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.8. 1-(1-Adamantyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid benzyl ester (**2a**). Yield: 0.55 g (72% from 0.50 g **2**); elemental Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_4$: C, 76.41; H, 7.05. Found: C, 76.19; H, 7.05; mp: 108–109 °C; ESI MS (+) ($\text{CH}_3\text{COCH}_3/\text{Na}^+$): m/z : 494.3 (100%, $[\text{M}+\text{Na}]^+$); ^1H NMR (CDCl_3 , ppm): 7.29–7.26 (vbr, 5H, $\text{CH}_{\text{phenyl}}$ together with solvent residual peak), 7.14 (d, $^3J_{\text{HH}} = 8$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.94 (d, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.79 (dd, $^3J_{\text{HH}} = 8$ Hz, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 5.11 (s, 2H, CH_2 benzyl), 3.77 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.05 (s, vbr, 9H, CH/CH_2 adamantyl), 1.72 (s, vbr, 6H, CH_2 adamantyl); ^{13}C [^1H] NMR (CDCl_3 , ppm): 186.0 (CO), 171.2 (CO), 154.8 ($\text{C}_{\text{indoleO}}$), 135.9 (C_{aromat}), 134.4 (C_{aromat}), 130.2 (C_{aromat}), 129.3 (C_{aromat}), 128.5 ($\text{CH}_{\text{phenyl}}$), 128.2 ($\text{CH}_{\text{phenyl}}$), 128.0 ($\text{CH}_{\text{phenyl}}$), 112.6 ($\text{C}_{\text{indoleH}}$), 111.5 ($\text{C}_{\text{indoleH}}$), 107.7 (C_{aromat}), 100.6 ($\text{C}_{\text{indoleH}}$), 66.6 (OCH_2), 55.7 (OCH_3), 46.6 ($\text{C}_{\text{adamantyl}}$), 39.3 (CH_2 adamantyl), 36.2 (CH_2 adamantyl), 30.6 (CH_2), 28.0 (CH adamantyl), 11.8 (CH_3); IR (selected, KBr, cm^{-1}): $\tilde{\nu} = 3091$ (w), 3062 (w), 3032 (w), 3005 (w), 2907 (s, $\nu(\text{C-H})$), 2850 (m), 2680 (w), 2658 (w), 2346 (w), 2067 (w), 1958 (w), 1879 (w), 1854 (w), 1831 (w), 1802 (w), 1734 (s, $\nu(\text{C}=\text{O})$), 1709 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.9. 1-(1-Carboxy-1,2-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid tert-butyl ester (**3o**). Yield: 0.37 g (76% from 0.30 g **3**); elemental Anal. Calcd for $\text{C}_{19}\text{H}_{31}\text{B}_{10}\text{NO}_4$: C, 51.22; H, 7.01. Found: C, 51.54; H, 6.99; mp: 109–110 °C; ESI MS (+) (CH_3COCH_3): m/z : 485.3 (100%, $[\text{M}+\text{K}]^+$); ^1H NMR (CDCl_3 , ppm): 7.31 (d, $^3J_{\text{HH}} = 8$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.95 (d, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.85 (dd, $^3J_{\text{HH}} = 8$ Hz, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 4.37 (s, 1H, $\text{C}_{\text{clusterH}}$), 3.85 (s, 3H, OCH_3), 3.52 (s, 2H, CH_2), 3.20–1.50 (m, vbr, 10H, $\text{C}_2\text{H}_{10}\text{B}_{10}$), 2.31 (s, 3H, CH_3), 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{11}B NMR (CDCl_3 , ppm): –1.2 (d, $^1J_{\text{BH}} = 180$ Hz, 1B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –2.6 (d, 1B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –8.5 (d, $^1J_{\text{BH}} = 154$ Hz, 2B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –11.9 (vbr, 3B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –13.1 (vbr, 3B, $\text{C}_2\text{H}_{10}\text{B}_{10}$); ^{13}C NMR (CDCl_3 , ppm): 169.9 (s, vbr, CO), 166.5 (s, CO), 155.9 (s, vbr, $\text{C}_{\text{indoleO}}$), 134.8 (s, vbr, C_{indole}), 130.2 (s, vbr, C_{indole}), 130.1 (s, vbr, C_{indole}), 113.2 (d, $^1J_{\text{CH}} = 161$ Hz, $\text{C}_{\text{indoleH}}$), 112.1 (s, vbr, C_{indole}), 112.0 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 5$ Hz, $\text{C}_{\text{indoleH}}$), 101.5 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 5$ Hz, $\text{C}_{\text{indoleH}}$), 81.2 (s, vbr, $\text{C}(\text{CH}_3)_3$), 74.6 (s, vbr, $\text{C}_{\text{cluster}}$), 59.3 (d, $^1J_{\text{CH}} = 191$ Hz, $\text{C}_{\text{clusterH}}$), 55.7 (q, $^1J_{\text{CH}} = 151$ Hz, OCH_3), 31.9 (t, $^1J_{\text{CH}} = 131$ Hz, CH_2), 28.0 (q, vbr, $^1J_{\text{CH}} = 131$ Hz, $\text{C}(\text{CH}_3)_3$), 11.4 (q, $^1J_{\text{CH}} = 131$ Hz, CH_3); IR (selected, KBr, cm^{-1}): $\tilde{\nu} = 3080$ (w), 3004 (w), 2978 (w), 2930 (w), 2831 (w), 2656 (w), 2574 (m, $\nu(\text{B-H})$), 1731 (s, $\nu(\text{C}=\text{O})$), 1719 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.10. 1-(1-Carboxy-1,7-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid tert-butyl ester (**3m**). Yield: 0.14 g (87% from 0.10 g **3**); elemental Anal. Calcd for $\text{C}_{19}\text{H}_{31}\text{B}_{10}\text{NO}_4$: C, 51.22; H, 7.01. Found: C, 51.41; H, 7.03; mp: 150–151 °C; ESI MS (+) ($\text{CH}_3\text{COCH}_3/\text{Na}^+$): m/z : 503.1 (100%, $[\text{M}+\text{CH}_3\text{COCH}_3]^+$), 468.1 (29%, $[\text{M}+\text{Na}]^+$); ^1H NMR (CDCl_3 , ppm): 7.24 (d, $^3J_{\text{HH}} = 8$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.94 (d, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.82 (dd, $^3J_{\text{HH}} = 8$ Hz, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 3.85 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2), 3.06 (s, 1H, $\text{C}_{\text{clusterH}}$), 3.30–1.40 (m, vbr, 10H, $\text{C}_2\text{H}_{10}\text{B}_{10}$), 2.27 (s, 3H, CH_3), 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{11}B NMR (CDCl_3 , ppm): –4.7 (d, $^1J_{\text{BH}} = 154$ Hz, 1B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –5.9 (d, 1B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –10.5 (d, $^1J_{\text{BH}} = 141$ Hz, 4B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –13.1 (d, $^1J_{\text{BH}} = 180$ Hz, 2B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –15.2 (d, $^1J_{\text{BH}} = 180$ Hz, 2B, $\text{C}_2\text{H}_{10}\text{B}_{10}$); ^{13}C NMR (CDCl_3 , ppm): 170.2 (s, CO), 167.3 (s, CO), 155.5 (s, vbr, $\text{C}_{\text{indoleO}}$), 134.6 (m, vbr, C_{indole}), 130.4 (m, vbr, C_{indole}), 129.6 (m, vbr, C_{indole}), 112.8 (d, $^1J_{\text{CH}} = 161$ Hz, $\text{C}_{\text{indoleH}}$), 111.7 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 6$ Hz, $\text{C}_{\text{indoleH}}$), 110.7 (m, vbr, C_{indole}), 101.1 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 6$ Hz, $\text{C}_{\text{indoleH}}$), 81.0 (m, vbr, $\text{C}(\text{CH}_3)_3$), 78.2 (vbr, $\text{C}_{\text{cluster}}$), 55.7 (q, $^1J_{\text{CH}} = 141$ Hz, OCH_3), 55.0 (d, vbr, $^1J_{\text{CH}} = 181$ Hz, $\text{C}_{\text{clusterH}}$), 31.9 (t, $^1J_{\text{CH}} = 121$ Hz, CH_2), 28.0 (q, $^1J_{\text{CH}} = 131$ Hz, $\text{C}(\text{CH}_3)_3$), 11.3 (q, $^1J_{\text{CH}} = 131$ Hz, CH_3); IR (selected, KBr, cm^{-1}): $\tilde{\nu} = 3056$ (m, $\nu(\text{C-H})$), 2978 (s, $\nu(\text{C-H})$), 2931 (s, $\nu(\text{C-H})$), 2834 (m), 2609 (s, $\nu(\text{B-H})$), 2066 (m), 1847 (m), 1728 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.11. 1-(1-Carboxy-1,12-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid tert-butyl ester (**3p**). Yield: 0.16 g (99% from 0.10 g **3**); elemental Anal. Calcd for $\text{C}_{19}\text{H}_{31}\text{B}_{10}\text{NO}_4$: C, 51.22; H, 7.01. Found: C, 51.14; H, 7.01; mp: 56–57 °C; ESI MS (+) (CH_3COCH_3): m/z : 503.3 (100%, $[\text{M}+\text{CH}_3\text{COCH}_3]^+$); ^1H NMR (CDCl_3 , ppm): 7.12 (d, $^3J_{\text{HH}} = 8$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.91 (d, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 6.79 (d, $^3J_{\text{HH}} = 8$ Hz, $^4J_{\text{HH}} = 2$ Hz, 1H, $\text{CH}_{\text{indole}}$), 3.84 (s, 3H, OCH_3), 3.48 (s, 2H, CH_2), 3.35–1.14 (m, vbr, 10H, $\text{C}_2\text{H}_{10}\text{B}_{10}$), 2.89 (s, 1H, $\text{C}_{\text{clusterH}}$), 2.18 (s, 3H, CH_3), 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3$); ^{11}B NMR (CDCl_3 , ppm): –13.0 (d, $^1J_{\text{BH}} = 154$ Hz, 5B, $\text{C}_2\text{H}_{10}\text{B}_{10}$), –15.1 (d, $^1J_{\text{BH}} = 180$ Hz, 5B, $\text{C}_2\text{H}_{10}\text{B}_{10}$); ^{13}C NMR (CDCl_3 , ppm): 170.2 (s, vbr, CO), 167.9 (s, CO), 155.3 (s, vbr, $\text{C}_{\text{indoleO}}$), 134.5 (s, vbr, C_{indole}), 130.5 (s, vbr, C_{indole}), 129.3 (s, vbr, C_{indole}), 112.7 (d, $^1J_{\text{CH}} = 161$ Hz, $\text{C}_{\text{indoleH}}$), 111.6 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 6$ Hz, $\text{C}_{\text{indoleH}}$), 110.2 (s, vbr, C_{indole}), 100.9 (dd, $^1J_{\text{CH}} = 161$ Hz, $^2J_{\text{CH}} = 6$ Hz, $\text{C}_{\text{indoleH}}$), 85.4 (s, vbr, $\text{C}_{\text{cluster}}$), 80.9 (s, vbr, $\text{C}(\text{CH}_3)_3$), 63.8 (d, $^1J_{\text{CH}} = 181$ Hz, $\text{C}_{\text{clusterH}}$), 55.7 (q, $^1J_{\text{CH}} = 141$ Hz, OCH_3), 31.9 (t, $^1J_{\text{CH}} = 121$ Hz, CH_2), 28.0 (q, vbr, $^1J_{\text{CH}} = 131$ Hz, $\text{C}(\text{CH}_3)_3$), 11.2 (q, $^1J_{\text{CH}} = 131$ Hz, CH_3); IR (selected, KBr, cm^{-1}): $\tilde{\nu} = 3059$ (w), 2925 (m, $\nu(\text{C-H})$), 2617 (s, $\nu(\text{B-H})$), 1728 (s, $\nu(\text{C}=\text{O})$).

4.1.2.2.12. *1-(1-Adamantyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid tert-butyl ester (3a)*. Yield: 0.16 g (67% from 0.15 g **3**); elemental Anal. Calcd for $C_{27}H_{35}NO_4$: C, 74.11; H, 8.06. Found: C, 74.12; H, 8.07; mp: 54–55 °C; ESI MS (+) (CH_3COCH_3/Na^+): m/z : 495.1 (100%, $[M+CH_3COCH_3]^+$); 1H NMR ($CDCl_3$, ppm): 7.14 (d, $^3J_{HH} = 8$ Hz, 1H, CH_{indole}), 6.97 (d, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 6.79 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 3.85 (s, 3H, OCH_3), 3.54 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.05 (s, vbr, 9H, CH/CH_2 adamantyl), 1.72 (s, vbr, 6H, CH_2 adamantyl), 1.41 (s, 9H, $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, ppm): 185.9 (CO), 170.7 (CO), 154.7 ($C_{indoleO}$), 134.1 (C_{indole}), 130.2 (C_{indole}), 129.2 (C_{indole}), 112.5 ($C_{indoleH}$), 111.3 ($C_{indoleH}$), 108.6 (C_{indole}), 100.8 ($C_{indoleH}$), 80.7 ($C(CH_3)_3$), 55.7 (OCH_3), 46.7 ($C_{adamantyl}$), 39.3 (CH_2 adamantyl), 36.2 (CH_2 adamantyl), 31.9 (CH_2), 28.1 ($C(CH_3)_3$), 28.0 (CH adamantyl), 11.9 (CH_3); IR (selected, KBr , cm^{-1}): $\tilde{\nu} = 2985$ (m, $\nu(C-H)$), 2934 (m, $\nu(C-H)$), 2854 (m), 2362 (w), 2344 (w), 1720 (m, $\nu(C=O)$).

4.1.2.3. Cleavage of the tert-butyl ester group. 4.1.2.3.1. *General procedure for 3o, m, p.* The respective tert-butyl ester **3** was dissolved in dichloromethane (1.5 mL/100 mg ester) and then TFA (0.5 mL/100 mg ester) was added and the solution stirred for 3 h at room temperature. Dichloromethane and excess of TFA were removed under reduced pressure. Recrystallization from dichloromethane yielded the products **4** as white solids.

4.1.2.3.2. *1-(1-Carboxy-1,2-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (4o)*. Yield: 0.14 g (92% from 0.16 g **3o**); elemental Anal. Calcd for $C_{15}H_{23}B_{10}NO_4$: C, 46.26; H, 5.95. Found: C, 46.04; H, 6.00; mp: 190–191 °C; ESI MS (–) (CH_3COCH_3): m/z : 777.6 (100%, $[2M-H]^-$); 1H NMR ($CDCl_3$, ppm): 7.31 (d, $^3J_{HH} = 8$ Hz, 1H, CH_{indole}), 6.93 (d, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 6.86 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 4.35 (s, 1H, $C_{clusterH}$), 3.84 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2), 3.37–1.50 (m, vbr, 10H, $C_2H_{10}B_{10}$), 2.30 (s, 3H, CH_3); ^{11}B NMR ($CDCl_3$, ppm): –2.4 (d, $^1J_{BH} = 141$ Hz, $C_2H_{10}B_{10}$), –8.5 (d, $^1J_{BH} = 141$ Hz, $C_2H_{10}B_{10}$), –12.0 (vbr, $C_2H_{10}B_{10}$), –12.6 (vbr, $C_2H_{10}B_{10}$); ^{13}C NMR ($CDCl_3$, ppm): 175.9 (s, vbr, CO), 166.6 (s, CO), 156.0 (s, vbr, $C_{indoleO}$), 135.3 (s, vbr, C_{indole}), 130.1 (s, vbr, C_{indole}), 129.9 (s, vbr, C_{indole}), 113.3 (d, $^1J_{CH} = 161$ Hz, $C_{indoleH}$), 112.2 (dd, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 5$ Hz, $C_{indoleH}$), 110.5 (s, C_{indole}), 101.4 (dd, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 5$ Hz, $C_{indoleH}$), 74.5 (m, vbr, $C_{cluster}$), 59.2 (d, vbr, $^1J_{CH} = 191$ Hz, $C_{clusterH}$), 55.8 (q, $^1J_{CH} = 141$ Hz, OCH_3), 29.9 (t, $^1J_{CH} = 131$ Hz, CH_2), 11.3 (q, $^1J_{CH} = 131$ Hz, CH_3); IR (selected, KBr , cm^{-1}): $\tilde{\nu} = 3397$ (w), 3068 (w), 3049 (m), 3009 (w), 2949 (m), 2913 (m), 2844 (w), 2729 (w), 2622 (m, $\nu(B-H)$), 2578 (s, $\nu(B-H)$), 1720 (s, $\nu(C=O)$), 1706 (s, $\nu(C=O)$). Structural data for **4o** obtained from dichloromethane at 4 °C as yellow prisms: $C_{15}H_{23}B_{10}NO_4$, $M_r = 389.44$, monoclinic, space group $P2_1/c$, $a = 1078.97(6)$, $b = 1681.67(7)$, $c = 1200.15(7)$ pm, $\beta = 112.316(7)^\circ$, $T = 130$ K, $V = 2.015(1)$ nm³, $Z = 4$, $\rho_{calcd} = 1.284$ Mg m^{–3}, $\mu = 0.080$ mm^{–1}, $3.04 < \theta < 30.51^\circ$, $R = 0.0473$, $wR = 0.0722$, $GOF = 0.726$.

4.1.2.3.3. *1-(1-Carboxy-1,7-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (4m)*. Yield: 0.12 g (98% from 0.14 g **3m**); elemental Anal. Calcd for $C_{15}H_{23}B_{10}NO_4$: C, 46.26; H, 5.95. Found: C, 46.20; H, 5.96; mp: 154–156 °C; ESI MS (–) (CH_3COCH_3/NH_3): m/z : 777.5 (100%, $[2M-H]^-$), 388.2 (35%, $[M-H]^-$), 344.3 (81%, $[M-CO_2H]^-$); 1H NMR ($CDCl_3$, ppm): 7.25 (d, $^3J_{HH} = 8$ Hz, 1H, CH_{indole}), 6.91 (d, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 6.82 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 3.83 (s, 3H, OCH_3), 3.63 (s, 2H, CH_2), 3.48–1.51 (m, vbr, 10H, $C_2H_{10}B_{10}$), 3.06 (s, 1H, $C_{clusterH}$), 2.26 (s, 3H, CH_3); ^{11}B NMR ($CDCl_3$, ppm): –4.7 (vbr, 2B, $C_2H_{10}B_{10}$), –10.4 (d, $^1J_{BH} = 141$ Hz, 4B, $C_2H_{10}B_{10}$), –13.1 (d, $^1J_{BH} = 180$ Hz, 2B, $C_2H_{10}B_{10}$), –15.2 (d, $^1J_{BH} = 180$ Hz, 2B, $C_2H_{10}B_{10}$); ^{13}C NMR ($CDCl_3$, ppm): 176.8 (s, vbr, CO), 167.3 (s, CO), 155.6 (s, vbr, $C_{indoleO}$), 135.1 (s, vbr, C_{indole}), 130.4 (s, vbr, C_{indole}), 129.3 (s, vbr, C_{indole}), 112.9 (d, $^1J_{CH} = 161$ Hz, $C_{indoleH}$), 111.9 (dd, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 5$ Hz, $C_{indoleH}$), 109.1 (s, vbr, C_{indole}),

101.0 (d, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 5$ Hz, $C_{indoleH}$), 78.0 (s, vbr, $C_{cluster}$), 55.8 (q, $^1J_{CH} = 141$ Hz, OCH_3), 55.0 (d, $^1J_{CH} = 181$ Hz, $C_{clusterH}$), 30.1 (t, $^1J_{CH} = 131$ Hz, CH_2), 11.3 (q, $^1J_{CH} = 131$ Hz, CH_3); IR (selected, KBr , cm^{-1}): $\tilde{\nu} = 3228$ (m), 3057 (m, $\nu(C-H)$), 2962 (w), 2839 (w), 2611 (s, $\nu(B-H)$), 1718 (s, $\nu(C=O)$). Structural data for **4m** obtained from *n*-pentane at 25 °C as yellow prisms: $C_{15}H_{23}B_{10}NO_4$, $M_r = 389.44$, monoclinic, space group $P2_1/c$, $a = 863.2(5)$, $b = 2180.5(5)$, $c = 1081.7(5)$ pm, $\beta = 103.147(5)^\circ$, $T = 130$ K, $V = 1.983(2)$ nm³, $Z = 4$, $\rho_{calcd} = 1.301$ Mg m^{–3}, $\mu = 0.081$ mm^{–1}, $2.60 < \theta < 30.51^\circ$, $R = 0.0434$, $wR = 0.1115$, $GOF = 0.942$.

4.1.2.3.4. *1-(1-Carboxy-1,12-dicarba-closo-dodecaboran(12)yl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (4p)*. Yield: 0.21 g (>99% from 0.24 g **3p**); elemental Anal. Calcd for $C_{15}H_{23}B_{10}NO_4$: C, 46.26; H, 5.95. Found: C, 46.04; H, 5.91; mp: 93–95 °C; ESI MS (–) (CH_3COCH_3): m/z : 777.5 (100%, $[2M-H]^-$); 1H NMR ($CDCl_3$, ppm): 7.13 (d, $^3J_{HH} = 8$ Hz, 1H, CH_{indole}), 6.89 (d, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 6.80 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 3.82 (s, 3H, OCH_3), 3.60 (s, 2H, CH_2), 3.36–1.47 (m, vbr, 10H, $C_2H_{10}B_{10}$), 2.90 (s, 1H, $C_{clusterH}$), 2.17 (s, 3H, CH_3); ^{11}B NMR ($CDCl_3$, ppm): –13.0 (d, $^1J_{BH} = 154$ Hz, 5B, $C_2H_{10}B_{10}$), –15.1 (d, $^1J_{BH} = 181$ Hz, 5B, $C_2H_{10}B_{10}$); ^{13}C NMR ($CDCl_3$, ppm): 176.8 (s, vbr, CO), 167.9 (s, CO), 155.4 (s, vbr, $C_{indoleO}$), 135.0 (s, vbr, C_{indole}), 130.5 (s, vbr, C_{indole}), 129.0 (s, vbr, C_{indole}), 112.7 (d, $^1J_{CH} = 151$ Hz, $C_{indoleH}$), 111.8 (dd, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 5$ Hz, $C_{indoleH}$), 108.6 (s, vbr, C_{indole}), 100.8 (dd, $^1J_{CH} = 161$ Hz, $^2J_{CH} = 5$ Hz, $C_{indoleH}$), 85.2 (s, vbr, $C_{cluster}$), 63.9 (d, $^1J_{CH} = 181$ Hz, $C_{clusterH}$), 55.8 (q, $^1J_{CH} = 141$ Hz, OCH_3), 30.0 (t, $^1J_{CH} = 131$ Hz, CH_2), 11.1 (q, $^1J_{CH} = 131$ Hz, CH_3); IR (selected, KBr , cm^{-1}): $\tilde{\nu} = 3430$ (w), 3061 (w), 3010 (w), 2926 (w), 2834 (w), 2621 (s, $\nu(B-H)$), 1709 (s, $\nu(C=O)$). Structural data for **4p** obtained from *n*-pentane at 25 °C as yellow prisms: $C_{15}H_{23}B_{10}NO_4 \cdot 0.5(C_5H_{12})$, $M_r = 425.25$, monoclinic, space group $C2/c$, $a = 2464.7(1)$, $b = 813.58(4)$, $c = 2306.98(8)$ pm, $\beta = 94.791(6)^\circ$, $T = 130$ K, $V = 4.6098(4)$ nm³, $Z = 8$, $\rho_{calcd} = 1.226$ Mg m^{–3}, $\mu = 0.075$ mm^{–1}, $2.46 < \theta < 25.35^\circ$, $R = 0.0483$, $wR = 0.1116$, $GOF = 0.898$.

4.1.2.4. Cleavage of the benzyl ester group. 4.1.2.4.1. *General procedure for 2a, m, p.* The respective benzyl ester **2** was dissolved in THF (3.5 mL/100 mg ester) and Pd (5 mol % on carbon) was added. The mixture was stirred for 24 h under H_2 atmosphere (10 bar) at room temperature. The solution was separated from the catalyst (either by normal filtration or through silica with hexanes/ethyl acetate) and concentrated *in vacuo*.

4.1.2.4.2. *1-(1-Adamantyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (4a)*. Yield: 0.13 g (80% from 0.20 g **2a**); elemental Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13. Found: C, 71.76; H, 7.16; mp: 99–100 °C; ESI MS (–) (CH_3COCH_3/NH_3): m/z : 380.1 (100%, $[M-H]^-$); 1H NMR ($CDCl_3$, ppm): 7.14 (d, $^3J_{HH} = 8$ Hz, 1H, CH_{indole}), 6.95 (d, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 6.79 (dd, $^3J_{HH} = 8$ Hz, $^4J_{HH} = 2$ Hz, 1H, CH_{indole}), 3.84 (s, 3H, OCH_3), 3.65 (s, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.05 (s, vbr, 9H, CH/CH_2 adamantyl), 1.72 (s, vbr, 6H, CH_2 adamantyl); $^{13}C\{^1H\}$ NMR ($CDCl_3$, ppm): 185.9 (CO), 176.8 (CO), 154.8 ($C_{indoleO}$), 134.6 (C_{indole}), 130.2 (C_{indole}), 128.9 (C_{indole}), 112.6 ($C_{indoleH}$), 111.4 ($C_{indoleH}$), 107.0 (C_{indole}), 100.5 ($C_{indoleH}$), 55.8 (OCH_3), 46.6 ($C_{adamantyl}$), 39.3 (CH_2 adamantyl), 36.2 (CH_2 adamantyl), 30.1 (CH_2), 28.0 (CH adamantyl), 11.7 (CH_3); IR (selected, KBr , cm^{-1}): $\tilde{\nu} = 3420$ (m), 2907 (s, $\nu(C-H)$), 2851 (m), 1707 (s, $\nu(C=O)$), 1688 (s, $\nu(C=O)$).

4.2. COX inhibition studies (determination of IC_{50} values)

Concentration-dependent inhibition reactions were performed by pre-incubating the inhibitor and enzyme for 17 min at 25 °C, followed by 3 min at 37 °C prior to the addition of 50 μ M [¹⁴C]-AA for 30 s at 37 °C. All assays were terminated and analyzed for substrate consumption by TLC as previously described.⁴⁴ All inhibitor concentrations for 50% enzyme activity (IC_{50}) were determined

graphically using Prism and were the average of at least two independent determinations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bmc.2012.05.063>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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