SUPPORTING INFORMATION:

Carboranyl analogues of mefenamic acid and their biological evaluation

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General procedure for halogenation

A dropping funnel was charged with 6–12 mL of a 1:1 (v/v) mixture of concentrated nitric acid (HNO₃) and concentrated sulfuric acid (H₂SO₄). A round-bottom three-neck flask equipped with a condenser was charged with the corresponding carborane isomer, halogen and glacial acetic acid. The funnel was connected to the flask. The mixture was gradually heated to 60 °C in an oil bath and the mixture of the acids was added dropwise over a period of 40–80 min. When the addition was completed, the resulting mixture was further stirred for 1–4.5 h at 80 °C until a slightly yellow and clear solution was formed. The reaction was monitored by TLC using n-hexane as eluent. After completion, the mixture was cooled to room temperature and diluted with ice-cold water. A white precipitate formed which was isolated by vacuum filtration. The crude product was further washed with water and then dissolved in diethyl ether. The resulting organic phase was treated with 10 mL aqueous solution of Na₂SO₃ (0.1 M). The organic phase was collected, dried over MgSO₄ and filtered. Evaporation of the solvent under reduced pressure gave the crude product as colorless powders. Further purification of the crude product was performed by column chromatography (silica gel, n-hexane/ethyl acetate, 1:0→4:1 (v/v)).

Characterization of the halogenated compounds

1. 9-Bromo-1,2-dicarba-closo-dodecaborane (2a)

9-Bromo-1,2-dicarba-closo-dodecaborane (2a) was synthesized from 2 (0.6 g, 4 mmol) and Br₂ (102.5 µL, 2 mmol) in 32 mL glacial acetic acid. 12 mL of the mixture of acids 1:1 (v/v) were added dropwise at 60 °C for 60 min and the reaction was further stirred for 1 h at 80 °C. Work-up gave a colorless solid. Yield 83% (0.738 g, 3.31 mmol). Calculated Mw 223.123 g/mol. Rf of 2a in mixture of n-hexane/ethyl acetate 7:3 (v/v) is 0.40. The spectroscopic data are in agreement with those reported in the literature.¹

Figure S1. ¹H-NMR spectrum of 2a in deuterated chloroform.

¹H-NMR (CDCl₃, 400 MHz): δ = 1.67–3.24 (br, 9H, BH), 3.60 (br s, 2H, CH-cluster) ppm.
Figure S2. $^{11}$B($^1$H)-NMR spectrum of 2a in deuterated chloroform.

$^{11}$B($^1$H)-NMR (CDCl₃, 128 MHz): $\delta$ = −15.8 (s, 2B, BH), −14.6 (s, 2B, BH), −13.6 (s, 2B, BH), −8.4 (s, 2B, BH), −1.7 (s, 1B, BH), 0.0 (s, 1B, BBr) ppm.

Figure S3. $^{11}$B-NMR spectra of 2a in deuterated chloroform.

$^{11}$B-NMR (CDCl₃, 128 MHz): $\delta$ = −15.8 (d, $J$ = 172.8 Hz, 2B), −14.5 (d, $J$ = 154.8 Hz, 2B), −13.6 (d, $J$ = 175.3 Hz, 2B), −8.4 (d, $J$ = 156.3 Hz, 2B), −1.7 (d, $J$ = 155.7 Hz, 1B), −0.01 (s, 1B, BBr) ppm.
2. 9-Iodo-1,7-dicarba-closo-dodecaborane (3a)

9-Iodo-1,7-dicarba-closo-dodecaborane (3a) was synthesized from 3 (0.3 g, 2.1 mmol) and I₂ (0.27 g, 1.05 mmol) in 16 mL glacial acetic acid. 6 mL of the mixture of acids 1:1 (v/v) were added dropwise at 60 °C for 40 min and the reaction was further stirred for 1 h at 80 °C. Work-up gave a colorless solid. Yield 97% (0.553 g, 2.04 mmol). Calculated Mw 270.123 g/mol. Rf of 3a in mixture of n-hexane: ethyl acetate 4:1 (v/v) is 0.65. The spectroscopic data are in agreement with those reported in the literature.²

Figure S4. ¹H-NMR spectrum of 3a in deuterated chloroform.

ÁH-NMR (CDCl₃, 400 MHz): δ = 1.64–3.38 (br, 9H, BH), 3.0 (br s, 2H, CH-cluster) ppm.

Figure S5 ¹¹B{¹H}-NMR spectrum of 3a in deuterated chloroform.

¹¹B{¹H}-NMR (CDCl₃, 128 MHz): δ = −23.5 (s, 1B, BI), −18.9 (s, 1B, BH), −16.8 (s, 2B, BH), −13.0 (s, 2B, BH), −11.9 (s, 1B, BH), −8.2 (s, 2B, BH), −5.4 (s, 1B, BH) ppm.
Figure S6. $^{11}$B-NMR spectrum of 3a in deuterated chloroform.

$^{11}$B-NMR (CDCl$_3$, 128 MHz): $\delta = -23.5$ (s, 1B, BI), $-18.9$ (d, $J = 182.9$ Hz, 1B), $-16.8$ (d, $J = 182.9$ Hz, 1B), $-13.0$ (d, $J = 158.7$ Hz, 2B), $-11.8$ (d, $J = 154.8$ Hz, 2B), $-8.2$ (d, $J = 154.3$ Hz, 1B), $-5.4$ (d, $J = 166.9$ Hz, 2B) ppm.

3. 2-Iodo-1,12-dicarba-closo-dodecaborane (4a)

2-Iodo-1,12-dicarba-closo-dodecaborane (4a) was synthesized from 4 (0.3 g, 2.1 mmol) and I$_2$ (0.27 g, 1.05 mmol) in 16 mL glacial acetic acid. 6 mL of the mixture of acids 1:1 (v/v) were added dropwise at 60 °C for 80 min and the reaction was further stirred for 4.5 h at 80 °C. Work-up gave a colorless solid. Yield 65% (0.369 g, 1.37 mmol). Calculated Mw 270.123 g/mol. Rf of 4a in mixture of n-hexane/ethyl acetate 4:1 (v/v) is 0.96. All the physical characteristics were identical to those reported in literature.

Figure S7. $^1$H-NMR spectrum 4a in deuterated chloroform.

$^1$H-NMR (CDCl$_3$, 400 MHz): $\delta = 1.66$-$2.8$ (br, 9H, BH), 2.89 (br s, 1H, CH-cluster), 3.21 (br s, 1H, CH-cluster) ppm.
Figure S8. $^{11}$B($^1$H)-NMR spectrum of 4a in deuterated chloroform.

$^{11}$B($^1$H)-NMR (CDCl$_3$, 128 MHz): $\delta = -28.4$ (s, 1B, BI), $-16.5$ (s, 1B, BH), $-14.3$ (s, 2B, BH), $-13.6$ (s, 4B, BH), $-11.9$ (s, 2B, BH) ppm.

Figure S9. $^{11}$B-NMR spectrum of 4a in deuterated chloroform.

$^{11}$B-NMR (CDCl$_3$, 128 MHz): $\delta = -28.5$ (s, 1B, BI), $-16.5$ (d, $J = 166.4$ Hz, 1B), $-14.3$ (d, $J = 167.7$ Hz, 2B), $-13.6$ (d, $J = 163.8$ Hz, 4B), $-11.9$ (d, $J = 181.7$ Hz, 2B) ppm.
4. 9-Iodo-1,2-dicarba-closo-dodecaborane

The title compound was synthesized from 2 (0.6 g, 4.2 mmol) and I₂ (0.5 g, 2.1 mmol) in 32 mL glacial acetic acid. 12 mL of the mixture of acids 1:1 (v/v) were added dropwise at 60 °C for 50 min and the reaction was further stirred for 1 h at 80 °C. The workup gave the product as colorless solid; yield 93% (1.06 g, 3.9 mmol). Calculated Mw 270.123 g/mol. Rᵣ of 9-I-1,2-C₂B₁₀H₁₁ in mixture of n-hexane: ethyl acetate 7:3 (v/v) is 0.47 and this spot in TLC is visible by staining in PdCl₂ solution in methanol as a black spot. The spectroscopic data agree with the literature.²

Figure S10. ¹H-NMR spectrum of 9-I-1,2-C₂B₁₀H₁₁ in deuterated chloroform.

¹H-NMR (CDCl₃, 400 MHz): δ = 1.72–3.37 (br, 9H, BH), 3.66 (br s, 1H, CH-cluster), 3.86 (br s, 1H, CH-cluster) ppm.

Figure S11. ¹¹B{¹H}-NMR spectrum of 9-I-1,2-C₂B₁₀H₁₁ in deuterated chloroform.

¹¹B{¹H}-NMR (CDCl₃, 128 MHz): δ = −16.6 (s, 1B, BI), −14.8 (s, 2B, BH), −13.5 (s, 2B, BH), −12.9 (s, 2B, BH), −7.5 (s, 2B, BH), −0.9 (s, 1B, BH) ppm.
**Figure S12.** $^{11}$B-NMR spectrum of 9-I-1,2-C$_{2}$B$_{10}$H$_{11}$ in deuterated chloroform.

$^{11}$B-NMR (CDCl$_{3}$, 128 MHz): $\delta$ = $-16.6$ (s, 1B, BI), $-14.8$ (d, $J = 177.9$ Hz, 2B), $-13.5$ (d, $J = 163.8$ Hz, 2B), $-12.8$ (d, $J = 170.2$ Hz, 2B), $-7.5$ (d, $J = 156.7$ Hz, 2B), $-0.9$ (d, $J = 155.0$ Hz, 1B) ppm.

**Nitrile derivatives 2b–4b**

5. N-(1,2-dicarba-closo-dodecaboran-9-yl)-2-benzonitrile (2b).

**Figure S13.** $^{1}$H-NMR spectrum of 2b in deuterated chloroform.

$^{1}$H-NMR (CDCl$_{3}$, 400 MHz): $\delta$ = 1.56 – 3.16 (br, 9H, BH), 3.47 (br s, 1H, CH-cluster), 4.40 (s, 1H, NH), 6.65 (t, $J = 8.0$ Hz, 1H, CH), 7.21-7.35 (m, 3H, CH) ppm.
**Figure S14.** $^{13}$C($^1$H)-NMR spectrum of 2b in deuterated chloroform.

$^{13}$C($^1$H)-NMR (CDCl$_3$, 101 MHz): $\delta = 43.5$ (CH, C-cluster), 50.3 (CH, C-cluster), 97.7 (C, C–1), 113.7 (CH, C–3), 116.8 (C, CN), 118.3 (CH, C–5), 132.6 (CH, C–6), 133.6 (CH, C–4), 150.9 (C, C–2) ppm.

**Figure S15.** $^{11}$B($^1$H)-NMR spectrum of 2b in deuterated chloroform.

$^{11}$B($^1$H)-NMR (CDCl$_3$, 128 MHz): $\delta = -16.7$ (s, 2B, BH), -15.7 (s, 2B, BH), -14.7 (s, 2B, BH), -9.7 (s, 2B, BH), -3.4 (s, 1B, BH), 7.8 (s, 1B, BN) ppm.
Figure S16. $^{11}$B-NMR spectrum of $2b$ in deuterated chloroform.

$^{11}$B-NMR (CDCl$_3$, 128 MHz): $\delta = -16.8$ (d, $J = 152.3$ Hz, 2B), $-15.7$ (d, $J = 130.5$ Hz, 2B), $-14.6$ (d, $J = 149.8$, 2B), $-9.7$ (d, $J = 151.1$ Hz, 2B), $-3.4$ (d, $J = 149.6$ Hz, 1B), 7.8 (s, 1B, BN) ppm.

Figure S17. HR-ESI-MS in of $2b$ in acetonitrile.

HR-ESI-MS (positive mode, in acetonitrile) $m/z [M+H]^+$: calculated 261.2386, found 261.2340; the observed isotopic pattern was in agreement with the calculated one.
Figure S18. HPLC analysis of 2b.

HPLC $t_R = 21.23$ min, purity: 99.5% relative area.

Figure S19. IR spectrum of 2b.

IR: $\tilde{\nu}$ (ATR): 3398 (m, NH), 3050 (s, CH-cluster), 2591 (s, BH), 2210 (m, CN), 1601–1430 (m-w, CC) and 751 (m, BB) cm$^{-1}$.
Molecular structure of 2b, ORTEP: displacement thermal ellipsoids are drawn at 50% probability level. 

*legend:* beige=B, black=C, white=H and yellow=N.
| **Table S1. Crystal data and structure refinement for 2b.** |
|----------------------------------------------------------|
| Empirical formula                                       | C₉H₁₆B₁₀N₂                        |
| Formula weight                                          | 260.34                           |
| Temperature                                             | 130(2) K                         |
| Wavelength                                              | 71.073 pm                        |
| Crystal system                                          | Triclinic                        |
| Space group                                             | P 1                              |
| Unit cell dimensions                                    |                                    |
| a = 684.48(8) pm                                        | α = 63.973(8)°                    |
| b = 1082.43(8) pm                                       | β = 78.281(9)°                    |
| c = 1091.27(9) pm                                       | γ = 78.968(8)°                    |
| Volume                                                  | 0.7066(1) nm³                     |
| Z                                                       | 2                                |
| Density (calculated)                                    | 1.224 Mg/m³                       |
| Absorption coefficient                                  | 0.062 mm⁻¹                       |
| F(000)                                                  | 268                              |
| Crystal size                                            | 0.40 x 0.15 x 0.02 mm³           |
| Theta range for data collection                         | 2.096 to 30.610°                 |
| Index ranges                                            | -9 ≤ h ≤ 9, -15 ≤ k ≤ 15, -15 ≤ l ≤ 15 |
| Reflections collected                                   | 8526                             |
| Independent reflections                                 | 3826 [R(int) = 0.0358]           |
| Completeness to theta = 28.285°                         | 99.7 %                           |
| Absorption correction                                   | Semi-empirical from equivalents   |
| Max. and min. transmission                              | 1.00000 and 0.86932              |
| Refinement method                                       | Full-matrix least-squares on F²   |
| Data / restraints / parameters                          | 3826 / 0 / 254                   |
| Goodness-of-fit on F²                                    | 1.030                            |
| Final R indices [I>2sigma(I)]                           | R1 = 0.0474, wR2 = 0.1143        |
| R indices (all data)                                    | R1 = 0.0687, wR2 = 0.1284        |
| Largest diff. peak and hole                             | 0.236 and -0.249 eÅ⁻³            |
| CCSD No.                                                | 2 154 849                        |
### Table S2. B–N coupling reactions of 9-I-1,2-C$_2$B$_{10}$H$_{11}$ with 2-amino-benzonitrile.

| 9-I-1,2-C$_2$B$_{10}$H$_{11}$ | Amine | Base | Pd catalyst/Ligand | Solvent | Time/Temp | % yield |
|-------------------------------|-------|------|-------------------|---------|-----------|---------|
| 1                             | 0.3 mmol | 1 eq. | KOt-Bu (1.2 eq.) | Pd(dba)$_2$ (20 mol%) / BINAP (20 mol%) | Dioxane (6 mL) | 90 h/95 °C | / |
| 2                             | 0.3 mmol | 2 eq. | K$_3$PO$_4$ (5 eq.) | Pd$_2$(dba)$_3$ (2.5 mol%) / BINAP (5 mol%) | Toluen (1.3 mL) | 45 h/100 °C | / |
| 3                             | 0.3 mmol | 2 eq. | KOt-Bu (5 eq.) | Pd(dba)$_2$ (5 mol%) / BINAP (5 mol%) | Dioxane (5 mL) | 1 h/rt | / |
| 4                             | 0.3 mmol | 3 eq. | K$_3$PO$_4$ (5 eq.) | Pd$_2$(dba)$_3$ (2.5 mol%) / DavePhos (5 mol%) | Toluen (1.3 mL) | 3 d/rt | / |
| 5                             | 0.3 mmol | 1 eq. | K$_3$PO$_4$ (1.6 eq.) | Pd$_2$(dba)$_3$ (10 mol%) / DavePhos (20 mol%) | Toluen (6 mL) | 22 h/95 °C | low |
| 6                             | 0.3 mmol | 1 eq. | K$_3$PO$_4$ (1.6 eq.) | Pd$_2$(dba)$_3$ (5 mol%) / DavePhos (10 mol%) | Toluen (3 mL) | 23 h/rt | low |
| 7                             | 0.3 mmol | 1 eq. | K$_3$PO$_4$ (1.6 eq.) | Pd$_2$(dba)$_3$ (5 mol%) / DavePhos (10 mol%) | Toluen (3 mL) | 6 d/100 °C | 22.0 |
| 8                             | 0.3 mmol | 3 eq. | K$_3$PO$_4$ (4 eq.) | SPhos-Pd-G3 (5 mol%) / SPhos (5 mol%) | Dioxane (1 mL) | 7 d/70 °C | / |
| 9                             | 0.3 mmol | 1 eq. | KOt-Bu (1.2 eq.) | Pd$_2$(dba)$_3$ (10 mol%) / BINAP (20 mol%) | Dioxane (8 mL) | 43 h/9 0°C | / |
| 10                            | 0.3 mmol | 1 eq. | K$_3$PO$_4$ (1 eq.) | Pd$_2$(dba)$_3$ (10 mol%) / BINAP (20 mol%) | Dioxane (8 mL) | 5 h/90 °C | / |

**Note:**
- dba = dibenzylideneacetone; BINAP = 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl; DavePhos = 2-dicyclohexylphosphino-2’-(N,N-dimethylamino)biphenyl; SPhos = 2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl; SPhos-Pd-G3 = (2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl) [2-(2’-amino-1,1’-biphenyl)]palladium(II) methanesulfonate

As is obvious from Table S2, the B–N coupling of the ortho isomer using 9-I-1,2-C$_2$B$_{10}$H$_{11}$ as a substrate was difficult or impossible because it took a long time at relatively high temperature: thus, many side products were formed besides the main product or no reaction occurred.
6. N-{1,7-dicarba-closo-dodecaboran-9-yl}-2-benzonitrile (3b)

**Figure S21.** ¹H-NMR spectrum of 3b in deuterated chloroform.

1H-NMR (CDCl₃, 400 MHz): δ = 1.91–3.26 (br, 9H, BH), 2.90 (br s, 2H, CH-cluster), 4.50 (s, 1H, NH), 6.68 (t, J = 7.9 Hz, 1H, CH), 7.29–7.38 (m, 3H, CH) ppm.

**Figure S22.** ¹³C{¹H} NMR spectrum of 3b in deuterated chloroform.

¹³C{¹H}-NMR (CDCl₃, 101 MHz): δ = 51.1 (CH, C-cluster), 97.8 (C, C–1), 113.8 (CH, C–3), 116.8 (C, CN), 118.2 (CH, C–5), 132.6 (CH, C–6), 133.6 (CH, C–4), 151.0 (C, C–2) ppm.
Figure S23. $^{11}$B-$^1$H-NMR spectrum of 3b in deuterated chloroform.

$^{11}$B-$^1$H-NMR (CDCl$_3$, 128 MHz): $\delta = -23.0$ (s, 1B, BH), $-19.1$ (s, 1B, BH), $-15.4$ (s, 2B, BH), $-14.3$ (s, 2B, BH), $-11.2$ (s, 1B, BH), $-7.5$ (s, 2B, BH), 1.4 (s, 1B, BN) ppm.

Figure S24. $^{11}$B-NMR spectrum of 3b in deuterated chloroform.

$^{11}$B-NMR (CDCl$_3$, 128 MHz): $\delta = -23.0$ (d, $J = 182.7$ Hz, 1B), $-19.1$ (d, $J = 182.5$ Hz, 1B), $-15.4$ (d, $J = 161.3$ Hz, 2B), $-14.2$ (d, $J = 153.6$ Hz, 2B), $-11.2$ (d, $J = 151.2$ Hz, 1B), $-7.5$ (d, $J = 162.8$ Hz, 2B), 1.4 (s, 1B, BN) ppm.
HR-ESI-MS (positive mode, in acetonitrile) $m/z \ [M+H]^+$: calculated 261.2386, found 261.2410; the observed isotopic pattern was in agreement with the calculated one.

**Figure S26. HPLC analysis of 3b.**

HPLC $t_R = 22.30$ min, purity: 98.9% relative area.
**Figure S27. IR spectrum of 3b.**

IR: $\tilde{\nu}$ (ATR): 3394 (m, NH), 3052 (s, CH-cluster), 2599 (s, BH), 2207 (m, CN), 1606–1429 (m-w, CC) and 754 (m, BB) cm$^{-1}$.

**Figure S28. Molecular structure of 3b.**

Molecular structure of 3b, ORTEP: displacement thermal ellipsoids are drawn at 50% probability level. **Legend:** beige–B, black–C, white–H and yellow–N.
Table S3. Crystal data and structure refinement for 3b.

| Property                                      | Value                          |
|-----------------------------------------------|--------------------------------|
| Empirical formula                             | C₉H₁₆B₁₀N₂                     |
| Formula weight                                | 260.34                         |
| Temperature                                   | 130(2) K                       |
| Wavelength                                    | 71.073 pm                      |
| Crystal system                                | Monoclinic                      |
| Space group                                   | P 2_/n                         |
| Unit cell dimensions                          | a = 1088.16(3) pm, α = 90°, b = 2043.39(4) pm, β = 111.384(3°), c = 1373.29(4) pm, γ = 90° |
| Volume                                        | 2.8433(1) nm³                  |
| Z                                             | 8                              |
| Density (calculated)                          | 1.216 Mg/m³                    |
| Absorption coefficient                        | 0.062 mm⁻¹                     |
| F(000)                                        | 1072                           |
| Crystal size                                  | 0.50 x 0.40 x 0.40 mm³         |
| Theta range for data collection               | 1.879 to 32.555°               |
| Index ranges                                  | -15 ≤ h ≤ 15, -30 ≤ k ≤ 29, -16 ≤ l ≤ 20 |
| Reflections collected                         | 30341                          |
| Independent reflections                       | 9505 [R(int) = 0.0457]         |
| Completeness to theta = 30.510°               | 100.0 %                        |
| Absorption correction                         | Semi-empirical from equivalents|
| Max. and min. transmission                    | 1.00000 and 0.96019            |
| Refinement method                             | Full-matrix least-squares on F²|
| Data / restraints / parameters                | 9505 / 0 / 507                 |
| Goodness-of-fit on F²                          | 1.041                          |
| Final R indices [I>2sigma(I)]                 | R1 = 0.0521, wR2 = 0.1156      |
| R indices (all data)                          | R1 = 0.0906, wR2 = 0.1318      |
| Largest diff. peak and hole                   | 0.309 and -0.242 eÅ⁻³          |
| CCSD No.                                       | 2 154 845                      |
7. $N\{1,12$-dicarba-closo-dodecaboran-2-yl$\}$-2-benzonitrile (4b)

Figure S29. $^1$H-NMR spectrum of 4b in deuterated chloroform

Figure S30. $^{13}$C($^1$H)-NMR spectrum of 4b in deuterated chloroform
Figure S31. $^{11}$B($^1$H)-NMR spectrum of 4b in deuterated chloroform.

$^{11}$B($^1$H)-NMR (CDCl$_3$, 128 MHz): $\delta = -20.4$ (s, 1B, BH), $-16.7$ (s, 2B, BH), $-15.7$ (s, 4B, BH), $-14.7$ (s, 2B, BH), $-4.0$ (s, 1B, BN) ppm.

Figure S32. $^{11}$B-NMR spectrum of 4b in deuterated chloroform.

$^{11}$B-NMR (CDCl$_3$, 128 MHz): $\delta = -20.5$ (d, $J = 169.8$ Hz, 1B), $-16.8$ (d, $J = 153.6$ Hz, 2B), $-15.7$ (d, $J = 138.2$ Hz, 4B), $-14.6$ (d, $J = 135.7$ Hz, 2B), $-3.9$ (s, 1B, BN) ppm.
Figure S33. HR-ESI-MS spectrum of 4b in acetonitrile, positive mode.

HR-ESI-MS (positive mode, in acetonitrile) m/z [M+H]+: calculated 261.2386, found 261.2360; the observed isotopic pattern was in agree with the calculated one.

Figure S34. HPLC analysis of 4b.

HPLC t_R = 24.83 min, purity: 98.6% relative area.
Figure S35. IR spectrum of 4b.

IR: \( \tilde{\nu} \) (ATR): 3363 (m, NH), 3052 (s, CH-cluster), 2602 (s, BH), 2215 (m, CN), 1603–1435 (m-w, CC) and 745 (m, BB) cm\(^{-1}\).

Figure S36. Molecular structure of 4b.

Molecular structure of 4b, ORTEP: displacement thermal ellipsoids are drawn at 50% probability level. Legend: beige–B, black–C, white–H and yellow–N.
Table S4. Crystal data and structure refinement for 4b.

| Property                                | Value                        |
|------------------------------------------|------------------------------|
| Empirical formula                        | C9H16B10N2                   |
| Formula weight                           | 260.34                       |
| Temperature                              | 130(2) K                     |
| Wavelength                               | 71.073 pm                    |
| Crystal system                           | Triclinic                    |
| Space group                              | P ̅1                         |
| Unit cell dimensions                     | a = 1010.92(5) pm, α = 67.991(7)°  |
|                                         | b = 1167.21(7) pm, β = 86.785(5)°  |
|                                         | c = 1329.5(1) pm, γ = 77.978(4)°  |
| Volume                                   | 1.4221(2) nm³                |
| Z                                        | 4                            |
| Density (calculated)                     | 1.216 Mg/m³                  |
| Absorption coefficient                   | 0.062 mm⁻¹                   |
| F(000)                                   | 536                          |
| Crystal size                             | 0.40 x 0.25 x 0.10 mm³       |
| Theta range for data collection          | 1.653 to 32.690°             |
| Index ranges                             | -13 ≤ h ≤ 15, -14 ≤ k ≤ 16, -14 ≤ l ≤ 19 |
| Reflections collected                    | 16335                        |
| Independent reflections                  | 9303 [R(int) = 0.0370]       |
| Completeness to theta = 30.510°          | 100.0 %                      |
| Absorption correction                    | Semi-empirical from equivalents |
| Max. and min. transmission               | 1.00000 and 0.99768          |
| Refinement method                        | Full-matrix least-squares on F² |
| Data / restraints / parameters            | 9303 / 0 / 507               |
| Goodness-of-fit on F²                    | 1.016                        |
| Final R indices [I>2sigma(I)]            | R1 = 0.0635, wR2 = 0.1246    |
| R indices (all data)                     | R1 = 0.1136, wR2 = 0.1489    |
| Largest diff. peak and hole              | 0.285 and -0.242 e-Å³        |
| CCSD No.                                 | 2 154 847                    |
Carboxylic acid derivatives 2c–4c

8. N-(1,2-dicarba-closo-dodecaboran-9-yl)-2-benzoic acid (2c)

Figure S37. $^1$H-NMR spectrum of 2c in deuterated acetone.

$^1$H-NMR ((CD$_3$)$_2$CO, 400 MHz): $\delta = 1.84$–2.98 (br, 9H, BH), 4.49 (br s, 2H, CH-cluster), 6.57 (m, 1H, CH), 7.29 (m, 2H, CH), 7.89 (m, 1H, CH), 8.05 (s, 1H, NH), 10.9 (br s, 1H, OH) ppm.

Figure S38. $^{13}$C($^1$H) NMR spectrum of 2c in deuterated acetone.

$^{13}$C($^1$H) NMR ((CD$_3$)$_2$CO, 101 MHz): $\delta = 44.3$ (CH, C-cluster), 51.9 (CH, C-cluster), 110.9 (C, C–1), 114.6 (CH, C–3), 114.9 (CH, C–5), 131.8 (CH, C–6), 133.8 (CH, C–4), 152.6 (C, C–2), 169.9 (C, COOH) ppm.
Figure S39. $^{11}$B{$^1$H}-NMR spectrum of 2c in deuterated acetone.

$^{11}$B{$^1$H}-NMR ((CD$_3$)$_2$CO, 128 MHz): $\delta = -16.5$ (s, 2B, BH), $-15.9$ (s, 2B, BH), $-14.6$ (s, 2B, BH), $-10.1$ (s, 2B, BH), $-4.1$ (s, 1B, BH), 7.8 (s, 1B, BN) ppm.

Figure S40. $^{11}$B-NMR spectrum of 2c in deuterated acetone.

$^{11}$B-NMR ((CD$_3$)$_2$CO, 128 MHz): $\delta = -16.2$ (d, $J = 186.9$ Hz, 2B), $-15.9$ (d, $J = 154.8$ Hz, 2B), $-14.6$ (d, $J = 167.6$ Hz, 2B), $-10.1$ (d, $J = 148.8$ Hz, 2B), $-4.1$ (d, $J = 147.7$ Hz, 1B), 7.8 (s, 1B, BN) ppm.
**Figure S41.** HR-ESI-MS spectrum of 2c in acetonitrile, negative mode.

HR-ESI-MS (negative mode, in acetonitrile) m/z [M-H]-: calculated 278.2184, found 278.2190; the observed isotopic pattern agreed with the calculated one.

**Figure S42.** HPLC analysis of 2c.

HPLC t_R = 16.62 min, purity: 98.5% relative area.
Figure S43. IR spectrum of 2c.

IR: $\tilde{\nu}$ (ATR): 3312 (m, NH), 3300–2500 (s, vbr, OH), 2922 (s, CH-cluster), 2611 (s, BH), 1643 (s, CO), 1576–1407 (m-w, CC) and 747 (m, BB) cm$^{-1}$.

Figure S44. Molecular structure of 2c.

Molecular structure of 2c, ORTEP: displacement thermal ellipsoids are drawn at 50% probability level. Legend: beige–B, black–C, white–H, yellow–N and blue–O.
### Table S5. Crystal data and structure refinement for 2c.

| Property                                      | Value                              |
|-----------------------------------------------|------------------------------------|
| **Empirical formula**                         | C_{9}H_{17}B_{10}NO_{2}            |
| **Formula weight**                            | 279.33                             |
| **Temperature**                               | 130(2) K                           |
| **Wavelength**                                | 71.073 pm                          |
| **Crystal system**                            | Monoclinic                         |
| **Space group**                               | P 2_{1}/c                           |
| **Unit cell dimensions**                      |                                    |
| a                                             | 832.82(3) pm                       |
| α                                             | 90°                                |
| b                                             | 1726.26(4) pm                      |
| β                                             | 94.549(2)°                         |
| c                                             | 2124.86(5) pm                      |
| γ                                             | 90°                                |
| **Volume**                                    | 3.0452(2) nm^{3}                   |
| Z                                             | 8                                  |
| **Density (calculated)**                      | 1.219 Mg/m^{3}                     |
| **Absorption coefficient**                    | 0.070 mm^{-1}                      |
| **F(000)**                                    | 1152                               |
| **Crystal size**                              | 0.40 x 0.40 x 0.40 mm^{3}          |
| **Theta range for data collection**           | 2.256 to 26.369°                   |
| **Index ranges**                              | -10 ≤ h ≤ 10, -21 ≤ k ≤ 21, -26 ≤ l ≤ 26 |
| **Reflections collected**                     | 25043                              |
| **Independent reflections**                   | 6228 [R(int) = 0.0363]             |
| **Completeness to theta = 25.242°**           | 99.9 %                             |
| **Absorption correction**                     | Semi-empirical from equivalents    |
| **Max. and min. transmission**                | 1.00000 and 0.56568                |
| **Refinement method**                         | Full-matrix least-squares on F^{2} |
| **Data / restraints / parameters**            | 6228 / 2 / 534                     |
| **Goodness-of-fit on F^{2}**                  | 1.017                              |
| **Final R indices [I>2sigma(I)]**             | R1 = 0.0622, wR2 = 0.1475          |
| **R indices (all data)**                      | R1 = 0.0855, wR2 = 0.1629          |
| **Largest diff. peak and hole**               | 0.340 and -0.334 eÅ^{-3}           |
| **CCSD No.**                                  | 2 154 850                          |

**Comments:** With intermolecular OH-O hydrogen donor acceptor bonds, a dimer is formed. A bond length analysis reveals a disorder between B11 and C11 with a ratio of 0.69(3) : 0.31 (3).
9. \(N\)-\(\{1,7\text{-dicarba-closo-dodecaboran-9-yl}\}\)-2- benzoic acid (3c)

**Figure S45.** \(^1\)H-NMR spectrum of 3c in deuterated chloroform.

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta = 1.56\text{–}2.98\) (br, 9H, BH), 2.87 (br s, 2H, CH-cluster), 6.63 (m, 1H, CH), 7.35 (m, 2H, CH), 7.85 (s, 1H, NH), 7.97 (m, 1H, CH), 10.4 (br s, 1H, OH) ppm.

**Figure S46.** \(^{13}\)C\(^{(1)}\)H\()-NMR spectrum of 3c in deuterated chloroform.

\(^{13}\)C\(^{(1)}\)H\()\)-NMR (CDCl\(_3\), 101 MHz): \(\delta = 29.7\) (CH, C-cluster), 50.9 (CH, C-cluster), 110.2 (C, C–1), 115.3 (CH, C–3), 115.4 (CH, C–5), 132.4 (CH, C–6), 134.8 (CH, C–4), 153.1 (C, C–2), 172.6 (C, COOH) ppm.
**Figure S47.** $^{11}$B($^1$H)-NMR spectrum of 3c in deuterated chloroform.

$^{11}$B($^1$H)-NMR (CDCl$_3$, 128 MHz): $\delta$ = –23.2 (s, 1B, BH), –19.1 (s, 1B, BH), –15.5 (s, 2B, BH), –14.2 (s, 2B, BH), –11.2 (s, 1B, BH), –7.4 (s, 2B, BH), 1.7 (s, 1B, BN) ppm.

**Figure S48.** $^{11}$B-NMR spectrum of 3c in chloroform.

$^{11}$B-NMR (CDCl$_3$, 128 MHz): $\delta$ = –23.6 (d, $J = 182.7$ Hz, 1B), –19.1 (d, $J = 182.0$ Hz, 1B), –15.5 (d, $J = 167.7$ Hz, 2B), –14.2 (d, $J = 168.9$ Hz, 2B), –11.2 (d, $J = 151.3$ Hz, 1B), –7.4 (d, $J = 160.8$ Hz, 2B), 1.7 (s, 1B, BN) ppm.
**Figure S49.** HR-ESI-MS spectrum of 3c in acetonitrile, negative mode.

![HR-ESI-MS spectrum](image)

HR-ESI-MS (negative mode, in acetonitrile) m/z [M-H]⁻: calculated 278.2184, found 278.2180; the observed isotopic pattern agreed with the calculated one.

**Figure S50.** HPLC analysis of 3c.

![HPLC analysis](image)

Signal 1: ADC1 A, ADC1 CHANNEL A

Signal 2: DAD1 A, Sig=254,16 Ref=off

| Peak | RetTime | Width | Area | Height | Area [mAU] | %     |
|------|---------|-------|------|--------|------------|-------|
| 1    | 15.897  | 0.2146| 3.7246| 2.89329e-1| 0.2561    |       |
| 2    | 17.938  | 0.2424| 3.68265| 2.53167e-1| 0.2532    |       |
| 3    | 18.400  | 0.1623| 1.44715356| 138.80160| 99.4908   |       |

Totals: 1454.56884 138.62410

HPLC $t_R = 18.40$ min, purity: 99.5% relative area.
Figure S51. IR spectrum of 3c.

IR: $\tilde{\nu}$ (ATR): 3304 (m, NH), 3300–2500 (s, vbr, OH), 3051 (s, CH-cluster), 2598 (s, BH), 1651 (s, CO), 1578–1408 (m-w, CC) and 742 (m, BB) cm$^{-1}$.

Figure S52. Molecular structure of 3c.

Molecular structure of 3c, ORTEP: displacement thermal ellipsoids are drawn at 50% probability level. 
Legend: beige–B, black–C, white–H, yellow–N and blue–O.
Table S6. Crystal data and structure refinement for 3c.

| Property                                | Value                  |
|-----------------------------------------|------------------------|
| Empirical formula                       | C9H17B10NO2            |
| Formula weight                          | 279.33                 |
| Temperature                             | 130(2) K               |
| Wavelength                              | 71.073 pm              |
| Crystal system                          | Monoclinic             |
| Space group                             | P 2\(\overline{1}\)/n   |
| Unit cell dimensions                    |                        |
| a                                       | 682.86(1) pm           |
| \(\alpha\)                               | 90°                   |
| b                                       | 1766.08(4) pm          |
| \(\beta\)                              | 101.373(2)°           |
| c                                       | 1246.95(3) pm          |
| \(\gamma\)                             | 90°                   |
| Volume                                  | 1.47427(5) \(\text{nm}^3\) |
| Z                                       | 4                      |
| Density (calculated)                    | 1.259 \(\text{Mg/m}^3\) |
| Absorption coefficient                  | 0.072 \(\text{mm}^{-1}\) |
| F(000)                                  | 576                    |
| Crystal size                            | 0.60 x 0.05 x 0.05 \(\text{mm}^3\) |
| Theta range for data collection         | 2.026 to 35.007°       |
| Index ranges                            | -10 \(\leq h \leq 10\), -28 \(\leq k \leq 27\), -19 \(\leq l \leq 19\) |
| Reflections collected                   | 30235                  |
| Independent reflections                 | 6078 [R(int) = 0.0424]  |
| Completeness to theta = 33.140°         | 100.0 %                |
| Absorption correction                   | Semi-empirical from equivalents |
| Max. and min. transmission              | 1.00000 and 0.93706    |
| Refinement method                       | Full-matrix least-squares on \(F^2\) |
| Data / restraints / parameters          | 6078 / 0 / 267         |
| Goodness-of-fit on \(F^2\)              | 1.012                  |
| Final R indices [I>2\(\sigma\)(I)]     | R1 = 0.0462, wR2 = 0.1165 |
| R indices (all data)                    | R1 = 0.0691, wR2 = 0.1295 |
| Largest diff. peak and hole             | 0.460 and -0.283 \(\text{e}\cdot\text{Å}^{-3}\) |
| CCSD No.                                | 2 154 846              |

Comments: With intermolecular OH-O hydrogen donor acceptor bonds, a dimer is formed.
10. *N*-\((1,12\text{-dicarba-closo-dodecaboran-2-yl})\)-2- benzoic acid (4c)

**Figure S53.** \(^1\)H-NMR spectrum of 4c in deuterated acetone.

\(^1\)H-NMR ((CD\(_3\))\(_2\)CO, 400 MHz): \(\delta = 0.90–3.0 \text{ (br, 9H, BH)}\), 3.47 (br s, 1H, CH-cluster), 3.77 (br s, 1H, CH-cluster), 6.74 (ddd, \(J = 8.1, 7.0, 1.2 \text{ Hz, 1H, CH}\)), 7.46 (ddd, \(J = 8.7, 7.0, 1.7 \text{ Hz, 1H, CH}\)), 7.57 (dd, \(J = 8.6, 1.2 \text{ Hz, 1H, CH}\)), 7.96 (dd, \(J = 8.0, 1.7 \text{ Hz, 1H, CH}\)), 8.42 (s, 1H, NH), 11.1 (br s, 1H, OH) ppm.

**Figure S54.** \(^1\)H-NMR spectrum of 4c in deuterated chloroform.

\(^1\)H-NMR (CDCl\(_3\), 400 MHz): \(\delta = 1.02–3.14 \text{ (br, 9H, BH)}\), 2.83 (br s, 1H, CH-cluster), 3.14 (br s, 1H, CH-cluster), 6.74 (ddd, \(J = 8.1, 7.0, 1.1 \text{ Hz, 1H, CH}\)), 7.44 (ddd, \(J = 8.7, 7.0, 1.7 \text{ Hz, 1H, CH}\)), 7.57 (dd, \(J = 8.6, 1.1 \text{ Hz, 1H, CH}\)), 7.99 (dd, \(J = 8.1, 1.7 \text{ Hz, 1H, CH}\)), 8.03 (s, 1H, NH) ppm; the proton of the COOH group is not visible.
Figure S55. $^{13}$C($^1$H)-NMR of 4c in deuterated acetone.

$^{13}$C($^1$H)-NMR ((CD$_3$)$_2$CO, 101 MHz): $\delta$ = 61.9 (CH, C-cluster), 73.0 (CH, C-cluster), 113.5 (C, C–1), 115.4 (CH, C–3), 116.5 (CH, C–5), 131.8 (CH, C–6), 134.2 (CH, C–4), 151.3 (C, C–2), 169.9 (C, COOH) ppm.

Figure S56. $^{13}$C($^1$H)-NMR spectrum of 4c in deuterated chloroform.

$^{13}$C($^1$H)-NMR (CDCl$_3$, 101 MHz): $\delta$ = 61.7 (CH, C-cluster), 68.3 (CH, C-cluster), 110.8 (C, C–1), 115.7(CH, C–3), 116.8 (CH, C–5), 132.4 (CH, C–6), 135.1 (CH, C–4), 152.0 (C, C–2), 173.0 (C, COOH) ppm.
**Figure S57.** $^{11}$B$^{[1H]}$-NMR spectrum of 4c in deuterated acetone.

$^{11}$B$^{[1H]}$-NMR ((CD$_3$)$_2$CO, 128 MHz): $\delta$ = –21.1 (s, 1B, BH), –16.9 (s, 2B, BH), –15.8 (s, 4B, BH), –14.6 (s, 2B, BH), –3.3 (s, 1B, BN) ppm.

**Figure S58.** $^{11}$B$^{[1H]}$-NMR of 4c in deuterated chloroform.

$^{11}$B$^{[1H]}$-NMR ((CDCl$_3$, 128 MHz): $\delta$ = –20.8 (s, 1B, BH), –16.8 (s, 2B, BH), –15.8 (s, 4B, BH), –14.6 (s, 2B, BH), –3.7 (s, 1B, BN) ppm.
Figure S59. $^{11}$B-NMR spectrum of 4c in deuterated acetone.

$^{11}$B-NMR ((CD$_3$)$_2$CO, 128 MHz): $\delta = -21.0$ (d, $J = 170.6$ Hz, 1B), $-16.9$ (d, $J = 153.6$ Hz, 2B), $-15.8$ (d, $J = 153.6$ Hz, 4B), $-14.6$ (d, $J = 157.4$ Hz, 2B), $-3.3$ (s, 1B, BN) ppm.

Figure S60. $^{11}$B-NMR spectrum of 4c in deuterated chloroform.

$^{11}$B-NMR ((CDCl$_3$, 128 MHz): $\delta = -20.7$ (d, $J = 181.3$ Hz, 1B), $-16.9$ (d, $J = 149.7$ Hz, 2B), $-15.7$ (d, $J = 151.0$ Hz, 4B), $-14.5$ (d, $J = 156.2$ Hz, 2B), $-3.7$ (s, 1B, BN) ppm.
HR-ESI-MS (negative mode, in acetonitrile) \( m/z \) [M-H]: calculated 278.2184, found 278.2190; the observed isotopic pattern agreed with the calculated one.

**Figure S62.** HPLC analysis of 4c.

HPLC \( t_R = 21.85 \) min, purity: 98.6% relative area.
Figure S63. IR spectrum of 4c.

IR: $\tilde{\nu}$ (ATR): 3304 (m, NH), 3300–2500 (s, vbr, OH), 2921 (s, CH-cluster), 2597 (s, BH), 1660 (s, CO), 1578–1403 (m-w, CC) and 741 (m, BB) cm$^{-1}$.

Figure S64. Molecular structure of 4c.

Molecular structure of 4c, ORTEP: displacement thermal ellipsoids are drawn at 50% probability level. Legend: beige–B, black–C, white–H, yellow–N and blue–O.
Table S7. Crystal data and structure refinement for 4c.

| Property                  | Value                                      |
|---------------------------|--------------------------------------------|
| Empirical formula         | C_{9}H_{17}B_{10}NO_{2}                   |
| Formula weight            | 279.33                                     |
| Temperature               | 130(2) K                                   |
| Wavelength                | 71.073 pm                                   |
| Crystal system            | Triclinic                                   |
| Space group               | P 1̅                                           |
| Unit cell dimensions      | a = 683.64(5) pm, α = 67.712(7)°           |
|                           | b = 1073.08(8) pm, β = 72.390(7)°          |
|                           | c = 1117.31(9) pm, γ = 86.659(6)°          |
| Volume                    | 0.7214(1) nm^3                             |
| Z                         | 2                                          |
| Density (calculated)      | 1.286 Mg/m^3                               |
| Absorption coefficient    | 0.073 mm\(^{-1}\)                         |
| F(000)                    | 288                                        |
| Crystal size              | 0.40 x 0.15 x 0.01 mm^3                    |
| Theta range for data collection | 2.055 to 28.239°          |
| Index ranges              | -9 ≤ h ≤ 8, -13 ≤ k ≤ 13, -14 ≤ l ≤ 13   |
| Reflections collected     | 6301                                       |
| Independent reflections   | 3001 [R(int) = 0.0400]                     |
| Completeness to theta = 25.350° | 100.0 %                           |
| Absorption correction     | Semi-empirical from equivalents            |
| Max. and min. transmission| 1.00000 and 0.98020                       |
| Refinement method         | Full-matrix least-squares on F^2           |
| Data / restraints / parameters | 3001 / 0 / 268                           |
| Goodness-of-fit on F^2    | 1.031                                      |
| Final R indices [I>2sigma(I)] | R1 = 0.0581, wR2 = 0.1023               |
| R indices (all data)      | R1 = 0.1053, wR2 = 0.1206                  |
| Largest diff. peak and hole | 0.203 and -0.231 e Å\(^{-3}\)             |
| CCSD No.                  | 2 154 848                                  |

Comments: With intermolecular OH-O hydrogen donor acceptor bonds, a dimer is formed. The carborane carbon atoms are disordered on two positions with a ratio of 0.53(2): 0.47(2).
Deboronation of 2b

11. Sodium rac-[N-(7,8-dicarba-closo-dodecaboran-6-yl)-2- benzonitrile] (5)

Figure S65. $^1$H-NMR spectrum of 5 in deuterated DMSO.

$^1$H-NMR ((CD$_3$)$_2$SO, 400 MHz): $\delta = 0.31$–1.75 (br, 8H, BH), 1.56 (br s, 1H, CH-cluster), 1.75 (br s, 1H, CH-cluster), 6.51 (s, 1H, NH), 7.18–7.31 (m, 4H, CH) ppm.

Figure S66. $^{11}$B($^1$H)-NMR spectrum of 5 in deuterated DMSO.

$^{11}$B($^1$H)-NMR ((CD$_3$)$_2$SO, 128 MHz): $\delta = -37.5$ (s, 1B, BH), -31.3 (s, 1B, BH), -24.2 (s, 1B, BH), -22.2 (s, 1B, BH), -21.2 (s, 1B, BH), -18.9 (s, 1B, BH), -14.1 (s, 1B, BH), -11.6 (s, 1B, BH), -0.6 (s, 1B, BN) ppm.
Figure S67. $^{11}$B-NMR spectrum of 5 in deuterated DMSO.

$^{11}$B-NMR ((CD$_3$)$_2$SO, 128 MHz): $\delta = -37.5$ (d, $J = 140.3$ Hz, 1B), $-31.3$ (d, $J = 119.1$ Hz, 1B), $-24.2$ (d, $J = 156.2$ Hz, 1B), $-22.2$ (d, $J = 131.8$ Hz, 1B), $-21.2$ (d, $J = 140.8$ Hz, 1B), $-18.9$ (d, $J = 161.3$ Hz, 1B), $-14.1$ (d, $J = 137.5$ Hz, 1B), $-11.6$ (d, $J = 134.6$ Hz, 1B), $-0.6$ (s, 1B, BN) ppm.

Figure S68. HR-ESI-MS spectrum of 5 in acetonitrile, negative mode.

HR-ESI-MS (negative mode, in acetonitrile) m/z $[M-\text{Na}]^{-}$: calculated 250.2212, found 250.2200; the observed isotopic pattern agreed with the calculated one.
Figure S69. HPLC analysis of 5.

HPLC $t_R = 17.53$ min, purity: 97.1% relative area.

Figure S70. IR spectrum of 5.

IR: $\tilde{\nu}$ (ATR): 3208 (m, NH), 2977 (s, CH-cluster), 2535 (s, BH), 2247 (w, CN), 1587–1455 (m-w, CC) and 756 (m, BB) cm$^{-1}$. 
Solubility and stability tests

The time-dependent experiments to determine the stability of the synthesized analogues at room temperature were performed by tracking the changes via $^1$H-NMR and $^{11}$B($^1$H)-NMR spectroscopy in DMSO-$d_6$. From the results, it could be concluded that the meta- (3b and 3c) and para- (4b and 4c) analogues were very stable as no changes were observed by NMR spectroscopy after 3 weeks. However, with the ortho analogues, especially 2b, deboronation occurred and the (very slow) formation of the respective nido species was observed after 24 h at room temperature. When stored as a solid at -20 °C, no decomposition was observed.

*Figure S71.* Time-dependent $^1$H-NMR spectra in deuterated DMSO for 3b at room temperature.

*Figure S72.* Time-dependent $^{11}$B($^1$H)-NMR spectra in deuterated DMSO for 3b at room temperature.
When it comes to solubility, it was mentioned in the main text that carboranes generally exhibit a very high hydrophobicity. This hydrophobicity increases following the order ortho, meta and para isomer. Thus, water solubility of carboranyl compounds may prove challenging. The synthesized carborane analogues (nitriles (2b–4b) and acids (2c–4c)) were not soluble in water and in 5 vol% aqueous solution of DMSO when 1 mM solutions were attempted to be prepared. To improve the solubility of the mentioned compounds in water, two different agents were used: BSA (bovine serum albumin) and 2-HP-ß-CD (2-hydroxypropyl-ß-cyclodextrin). In both cases, the solubility of the carboranyl analogues was improved when a 1:1 mixture of products with BSA or a 1:10 mixture of products with 2-HP-ß-CD were prepared in 1 vol% DMSO, using PBS (phosphate-buffered saline, pH 7.4) as dilution solvent. When the stock solutions of the acids (2c–4c) and the nido analogue (5) in DMSO (2 mM) were diluted with aqueous PBS, a clear solution was observed even without solubilizing agent, while for the nitriles (2b–4b) the presence of the additive was fundamental to result in clear solutions.

Figure S74. Solubility screening of 3b with BSA (left) and 2-HP-ß-CD (right).

Photo taken by L.U.
Modelling the interaction of carboranyl analogues of mefenamic acid with the solubilizing agents

The crystal structures of the ortho- and meta-carborane derivatives (2b, 3b) were available. In order to estimate the effect of the carborane clusters on the binding to the solubilizing agents, the adamantane analogues of 2b and 3b (A1b and A2b, Figure S76) were created with Avogadro\textsuperscript{7} and optimized at the PM6-D3H4X level of theory using MOPAC.\textsuperscript{8} The adamantane was functionalized either at the secondary (C2) position (A1b) or at the tertiary (C1) position A2b. The docking into the bovine serum albumin (BSA) protein structure (PDB ID: 4OR0)\textsuperscript{9} and 2-hydroxypropyl-\(\beta\)-cyclodextrin (2-HP-\(\beta\)-CD)\textsuperscript{10} was performed/evaluated using Autodock 4.2.\textsuperscript{11} In the first docking run, the whole BSA structure was included in the grid box to locate a favorable binding site. A 40 × 40 × 40 grid box was centered around the 2-HP-\(\beta\)-CD host molecule. A 0.375 Å grid spacing was used throughout. A Lamarckian genetic algorithm was used to generate 100 docked conformations.\textsuperscript{12} Otherwise default Autodock 4.2 settings were used.

The most populated and lowest energy conformers docked into the BSA protein were all located in the FA6 binding site (Figure S77).\textsuperscript{13} The lowest energy and most populated conformation for 3b, with a 57% distribution had a mean binding energy of -8.62 kcal/mol. The lowest energy conformation of 2b had a mean binding energy of -8.31 kcal/mol, but only 22% of the docked poses were in this conformation. The most populated conformation of 2b (53%) had a higher mean binding energy of -7.45 kcal/mol. The adamantane analogues populated the same binding pocket but with energy values of only -2.93 kcal/mol (A2b) and -3.18 kcal/mol (A1b). The FA6 binding site represents a low affinity binding site. No specific binding motive was expected.\textsuperscript{13} Both 2b and 3b are located between hydrophobic residues and the R208-D323-E353 salt bridge (Figure S77). The adamantane analogues A1b and A2b were rotated in the pocket and their nitrile groups formed a hydrogen bond with K350.
Figure S77. 3b (A) and A2b (B) docked into the FA6 pocket of BSA. Selected BSA side chain residues and receptor-ligand interactions are labelled.

Only a few conformers were found during docking into 2-HP-β-CD. All conformers bound to the center of the 2-HP-β-CD molecule (Figure S78). The ligands only differed in their rotation within the 2-HP-β-CD ring. The mean binding energies of 2b and 3b (-9.96 and -9.86 kcal/mol, respectively) were lower than for A1b and A2b (-4.52 and -3.91 kcal/mol, respectively). All ligand nitrile groups formed hydrogen bonds with the hydroxyl groups of the CD ring. The more hydrophobic portion of 2-HP-β-CD was favored by the carborane and adamantane residues.

Figure S78. 3b (left) and A2b (right) docked in 2-HP-β-CD. Selected guest-host interactions are labelled.

In summary, approximately 2.5 times lower binding energies were predicted for the carborane derivatives, compared to the adamantane analogues (for binding to both BSA and 2-HP-β-CD). The carborane derivatives seemed to bind stronger to the host molecules than the respective adamantane analogues. These results are in agreement with the experimentally observed trends for association constants of carborane and adamantane derivatives with β-cyclodextrin. Strong binding of the carboranyl analogues of mefenamic acid...
to the also present solubilizing agents could explain the observed loss of inhibitory activity (see main text for details).

COX inhibition

COX inhibition in the absence of BSA

Figure S79. Inhibition of COX-1 (left) and COX-2 (right) by 5 in the concentration range between 0.32-320 µM.

Figure S80. Inhibition of COX-1 (left) and COX-2 (right) by mefenamic acid (1) in the concentration range between 0.01-100 µM.

COX inhibition in the presence of BSA

Based on the evaluation of bovine serum albumin as solubilizer for the carboranyl derivatives as discussed above, we performed COX inhibition studies in the presence of BSA to test its influence on COX inhibition results and to evaluate its applicability for less soluble compounds within this assay. Initially, COX inhibition was evaluated in the presence of a final concentration of 2 mM BSA for COX-1 and COX-2, which resembled a high concentration as needed for applying an excess of BSA compared to the inhibitors that are usually tested in concentrations of up to 100-320 µM. For that, BSA was dissolved in assay buffer and the BSA mixture (150 µL, 2.66 mM) was used instead of blank assay buffer. Subsequently, the further assay reagents (hemin, COX, DMSO, ADHP and arachidonic acid, in sum 50 µL) were added according to the manufacturer’s protocol and the assay was performed. The results showed that a high concentration of 2 mM BSA in the assay buffer apparently completely blocked COX inhibition and hence was not suitable (Table S8).

Table S8. COX-2 inhibition in the presence or absence of bovine serum albumin (BSA).

|                         | % Inhibition COX-1* | % Inhibition COX-2* |
|-------------------------|---------------------|---------------------|
| Blank (DMSO)            | n.i.                | n. i.               |
| Blank (DMSO), 2 mM BSA  | 101/100             | 99/115              |

*% inhibition values lower than 5% or negative values compared to the initial activity in the absence of inhibitor were interpreted as ‘no inhibition’ (n. i.)
Based on these results, we aimed to determine the BSA concentration, which was still tolerated under assay conditions, and investigated COX-1 inhibition in the presence of decreasing concentrations of BSA. For that, a stock solution 200 µM BSA in assay buffer was prepared and 10-fold diluted to the following concentrations: 20 µM, 2 µM, 0.2 µM, 0.02 µM, and 0.002 µM. To 100 µL of the respective BSA stock solution placed in the well was added 70 µL of a premixed solution of assay buffer/heme/COX-1 (50/10/10 v/v/v) followed by addition of the residual reagents (in sum 30 µL) according to the manufacturer’s protocol to achieve final concentrations between 0.001 µM and 100 µM BSA in the assay. BSA showed complete apparent inhibition at 100 µM while lower concentrations than 10 µM did not interfere with the COX inhibition assay (Figure S80, left). A more detailed screening was performed by further dilution of BSA stock solution to achieve final concentrations of 10 / 20 / 50 / 60 / 80 µM BSA in the assay which gave an IC₅₀(COX-1) of approximately 50 µM for BSA (Figure S80, right). For comparison, also a directly prepared 20 µM BSA solution in assay buffer leading to a final BSA concentration of 10 µM BSA in the assay showed no apparent inhibition and hence did not interfere with the COX assay.

Figure S81. Inhibition of COX-1 in the presence of BSA in the concentration range between 0.001-100 µM (left) and 0.1-100 µM (right).

COX-1 inhibition in the absence and presence of constantly 1 µM BSA was determined for the reference SC560, a selective COX-1 inhibitor showing 50% COX inhibition at around 5 nM as given by the manufacturer. IC₅₀(COX-1) of 20 nM determined in the absence of BSA (Figure S82A) was in good agreement to the IC₅₀(COX-1) of 17 nM determined in the presence of constantly 1 µM BSA (Figure S82B). Also, inhibition of 10 nM SC560 in the presence of 0.001-1 µM BSA (Figure S82C) was found to be in the range of 19-30% and hence comparable.
**Figure S82.** Inhibition of COX-1 by 0.003-1 µM SC560 in the absence of BSA (A), by 0.003-0.1 µM SC560 in the presence of 1 µM BSA (B), and by 0.01 µM SC560 in the presence of 0.001-1 µM BSA (C, mean of all experiments is shown as dotted horizontal line).

Next, we determined the COX-1 inhibition of 3b, 4b, and 5 in the presence and absence of 10 µM BSA (Table S9). While 3b and 4b did not show inhibition in both cases, the inhibition of 5 was not influenced by the presence of 10 µM BSA.

**Table S9.** COX-2 inhibition in the presence or absence of bovine serum albumin (BSA).

|                  | % Inhibition COX-1* |
|------------------|---------------------|
| 3b (100 µM)      | n.i.                |
| 3b (100 µM), 10 µM BSA | n.i.              |
| 4b (100 µM)      | n.i.                |
| 4b (100 µM), 10 µM BSA | n.i.              |
| 5 (100 µM)       | 85                  |
| 5 (100 µM), 10 µM BSA | 73/86             |

*% inhibition values lower than 5% or negative values compared to the initial activity in the absence of inhibitor were interpreted as ‘no inhibition’ (n. i.)

Of note, we observed slightly higher inhibition values for BSA in experiments where BSA in assay buffer was mixed with heme first followed by addition of COX (Table S10). In these experiments, BSA in assay buffer (1.33 nM, 133 nM, 2.66 µM) was mixed with heme followed by COX in the ratio 150/10/10 (v/v/v), then 170 µL were placed in each well and the residual reagents (in sum 30 µL) were added according to the manufacturer’s protocol. In this case, already in the presence of 2 µM BSA the COX-1 inhibition was at 21-25 % while a lower concentration of 1 or 100 nM BSA was better tolerated. Investigation of compounds 3b, 4b and 5 was hence performed at a lower concentration of BSA and hence excess of inhibitor. This however revealed a similar picture: while 3b and 4b did not show considerable COX-1 or COX-2 inhibition, 5 was also in this setup identified as inhibitor of COX-1.
### Table S10. COX inhibition in the presence of bovine serum albumin (BSA)**.

|                                      | % Inhibition COX-1* | % Inhibition COX-2* |
|--------------------------------------|---------------------|---------------------|
| Blank (DMSO), 2 µM BSA              | 21 / 25             | n.d.                |
| Blank (DMSO), 100 nM BSA            | 2 / 10              | 5 / 36              |
| 3b (100 µM), 100 nM BSA             | 11 / 17             | 27 / 24             |
| 4b (100 µM), 100 nM BSA             | 9 / 14              | 6 / 13              |
| 5 (100 µM), 100 nM BSA              | 89 / 89             | n.d.                |
| Blank (DMSO), 1 nM BSA              | n.i. / n.i.         | n. i. / 16          |
| Celecoxib 1 µM, 1 nM BSA            | n.d.                | 88                  |
| 3b (1 µM), 1 nM BSA                 | n.i. / 11           | 5 / 2               |
| 4b (1 µM), 1 nM BSA                 | 3 / 6               | n.i. / 15           |
| 5 (1 µM), 1 nM BSA                  | 5 / 17              | 15 / 16             |

* n.i.….% inhibition values lower than 5% or negative values compared to the initial activity in the absence of inhibitor were interpreted as ‘no inhibition’; n.d. … not determined; **BSA stock solutions were prepared based on a 1 mg/mL (15 µM) stock solution of BSA in assay buffer by dilution as further given in the text.

In conclusion, principally COX inhibition could be determined in the presence of BSA as solubilizer, and in this study, we observed no clear inhibition differences in the presence or absence of BSA. However, the applicable concentration range for BSA was found to be limited to maximal 10 µM BSA under optimized conditions, which is still markedly lower, compared to the highest applied inhibitor concentrations which are typically in the range of 100-320 µM. Hence, only excess of inhibitor compared to BSA can be investigated at higher concentrations and potential adverse effects of strong inhibitor binding to serum albumin on COX inhibition must always be considered.

### Cytotoxicity results

To elevate the solubility of experimental drugs, two protocols already described in literature\textsuperscript{15,16} and based on using 2-HP-β-CD or BSA as solubilizers were applied. For the purpose of improving the solubility of tested compounds, 2-HP-β-CD was added in the following ratio: [Compound]:[2-HP-β-CD] = 1:8. (C, D) CT26 (4 × 10\textsuperscript{3}/well) and HCT116 (5 × 10\textsuperscript{3}/well) were treated for 72 h with indicated compounds. BSA was added in [Compound]:[BSA] = 1:1 ratio. Despite the potential to enhance the solubility of compounds, their antitumor properties were significantly diminished. As presented in Figure S79, IC\textsubscript{50} values after application of the mentioned solubility protocols were not detected. In concordance with our data, Djajadisastra et al. showed that mefenamic acid (Mefa) is able to bind to BSA\textsuperscript{17} and that BSA is able to neutralize the activity of other drugs.\textsuperscript{18} In summary, it can be concluded that for in vitro investigation improvement of the drugs’ solubility by using BSA or 2-HP-β-CD can seriously interfere with the drugs’ efficacy and, therefore, it is contraindicated as an approach for solubility improvement.
Figure S83. Using 2-HP-β-CD and BSA to improve solubility diminished antitumor activity of mefenamic acid (1) and its carborane-containing analogues in vitro.

(A, B) CT26 (4 × 10^3/well), HT-29 (1.5 × 10^4/well), SW480 (3 × 10^3/well) and colorectal HCT116 (5 × 10^3/well) cell lines were treated for 72h with a range of doses of indicated compounds. Cell viability in all experiments was determined by MTT assay and results are presented as mean ± SD.
**Figure S84.** The effect of mefenamic acid (1) and its carborane-containing analogues on colon cancer cells in vitro.

Mouse colon carcinoma cell line CT26 (4 × 10^3/well), human colorectal adenocarcinoma cell lines HT-29 (1.5 × 10^4/well) and SW480 (3 × 10^4/well), and human colorectal carcinoma cell line HCT116 (5 × 10^3/well) were treated for 72 h with a range of doses of indicated compounds. Cell viability was determined by MTT and CV assays. Representative data from three independent experiments are shown here as the mean ± SD.
**Figure S85.** Induction of cytoprotective autophagy.

(A) HCT116 and (B) SW480 cells were treated with IC$_{50}$ dose of tested compounds for 72 h (HCT116) or 48 h (SW480) before autophagosomes were detected by AO supravital staining. The outcome of induced autophagy was determined by assessment of cellular viability after concurrent treatment of HCT116 cells (C) and SW480 cells (D) with IC$_{50}$ dose of tested compounds and autophagy inhibitor chloroquine (20 µM) for 72 h (HCT116) or 48 h (SW480). *p<0.05, **p<0.01; Student’s t-test.

**Table S10.** IC$_{50}$ values (µM) of compounds tested on mouse peritoneal macrophages.

| Cells | Peritoneal macrophages |
|-------|------------------------|
|       |                        |
|       | +                      |
| MTT   | CV                     |
| 1     | 182 ± 2.9              | >200          |
| 2b    | 42 ± 0.0               | >200          |
| 3b    | 35.4 ± 2.5             | 38.5 ± 0.8    |
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