SUPPORTING INFORMATION FOR:

Discovery of N-hydroxyindole-based inhibitors of human lactate dehydrogenase isoform A (LDH-A) as starvation agents against cancer cells.

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Experimental Section

Chemistry. Commercially available chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification. NMR spectra were obtained with a Varian Gemini 200 MHz spectrometer. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced from solvent references. Electron impact (EI, 70 eV) mass spectra were obtained on a Thermo Quest Finningan (TRACE GCQ plus MARCA) mass spectrometer. Purity was routinely measured by HPLC on a Waters SunFire RP 18 (3.0 x 150 mm, 5 µm) column (Waters, Milford, MA, www.waters.com) using a Beckmann SystemGold instrument consisting of chromatography 125 Solvent Module and a 166 UV Detector. Mobile phases: 10 mM ammonium acetate in Millipore purified water (A) and HPLC grade acetonitrile (B). A gradient was formed from 5% to 80% of B in 10 minutes and held at 80% for 10 min; flow rate was 0.7 mL/min and injection volume was 30 µL; retention times (HPLC, tR) are given in minutes. Compound HPLC purity was determined by monitoring at 254 and 300 nm and was found in the range 96-99%, unless otherwise noted. Chromatographic separations were performed on silica gel columns by flash (Kieselgel 40, 0.040–0.063 mm; Merck) or gravity column (Kieselgel 60, 0.063–0.200 mm; Merck) chromatography. Reactions were followed by thin-layer chromatography (TLC) on Merck aluminum silica gel (60 F254) sheets that were visualized under a UV lamp. Evaporation was performed in vacuo (rotating evaporator). Sodium sulfate was always used as the drying agent. Microwave assisted reaction were run in a CEM or Biotage microwave synthesizer. Precursors 2a-f are commercially available, whereas 2g1 was previously reported.

5-(4-Methyl-3-nitrophenyl)-1H-tetrazole (2k). According to Sharpless’ synthesis of tetrazoles,2 benzonitrile 6 (500 mg, 3.08 mmol) was dissolved in water (6 mL) and treated with sodium azide (221 mg, 3.39 mmol) and zinc bromide hydrate (694 mg, 3.08 mmol). The resulting suspension was refluxed for 36 h, then treated with aqueous 3 N HCl (until pH 1) and EtOAc. Stirring was continued until all the white solid was dissolved. The organic phase was separated and the water
phase was extracted again with EtOAc. The combined organic phase was concentrated and the residue was recovered with aqueous 0.25 N NaOH and stirred for 30 min. The suspension was filtered to remove Zn(OH)$_2$ and the resulting solution was acidified with 3 N HCl to precipitate the tetrazole derivative. The solid was then dissolved in EtOAc and MeOH and the solution was dried and concentrated to give pure 2k (571 mg, 90 % yield); $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 2.61 (s, 3H), 7.76 (d, 1H, $J = 7.9$ Hz), 8.32 (dd, 1H, $J = 8.1, 1.8$ Hz), 8.67 (d, 1H, $J = 1.6$ Hz).

**General procedure for the preparation of ketoesters 3a-g.** Nitrotoluene derivatives 2a-g (8.5 mmol) and dimethyl oxalate (5.00 g, 42.3 mmol) were dissolved in anhydrous DMF (15 mL) and the resulting solution was added dropwise under nitrogen to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 4.0 equiv) in DMF (20 mL) at 0 °C. The mixture was stirred at RT until consumption of starting material (TLC, 4-24 h), then it was diluted with 1N HCl or saturated aqueous NH$_4$Cl, and extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography using the indicated eluant, to give the ketoesters.

**Methyl 3-(2-nitrophenyl)-2-oxopropanoate (3a).** (61% yield from 2a) $R_f = 0.26$ (n-hexane/EtOAc 7:3); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 3.95 (s, 3H), 4.54 (s, 2H), 7.31-7.68 (m, 3H), 8.18 (dd, 1H, $J = 8.2, 1.5$ Hz); signals imputable to the enol form (~ 30%) $\delta$ (ppm): 3.94 (s, 3H), 6.63 (bs, 1H, exchangeable), 6.93 (s, 1H), 7.91 (dd, 1H, $J = 8.1, 1.4$ Hz), 8.23 (dd, 1H, $J = 8.1, 1.5$ Hz).

**Methyl 3-(2-methyl-6-nitrophenyl)-2-oxopropanoate (3b).** (75% yield from 2b) $R_f = 0.33$ (n-hexane/EtOAc 7:3); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 2.36 (s, 3H), 3.93 (s, 3H), 4.44 (s, 2H), 7.35 (t, 1H, $J = 7.9$ Hz), 7.50 (d, 1H, $J = 7.3$ Hz), 7.86 (d, 1H, $J = 8.1$ Hz); signals imputable to the enol form (~ 10%) $\delta$ (ppm): 6.08 (bs, 1H, exchangeable), 6.73 (s, 1H), 7.75 (d, 1H, $J = 7.7$Hz).

**Methyl 3-(2-nitro-6-(trifluoromethyl)phenyl)-2-oxopropanoate (3c).** (87% yield from 2c) $R_f = 0.40$ (n-hexane/EtOAc 7:3); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 3.96 (s, 3H), 4.69 (s, 2H), 7.66 (t, 1H, $J =$
8.1 Hz), 8.02 (d, 1H, J = 7.9 Hz), 8.26 (d, 1H, J = 8.2 Hz); signals imputable to the enol form (~10%) δ (ppm): 3.96 (s, 3H), 6.14 (bs, 1H, exchangeable), 6.78 (q, 1H, J = 2.2 Hz), 7.57 (t, 1H, J = 8.2 Hz), 7.93 (d, 1H, J = 7.9 Hz).

**Methyl 3-(2-chloro-6-nitrophenyl)-2-oxopropanoate (3d).** (78% yield from 2d) R_f = 0.24 (n-hexane/EtOAc 8:2); ^1^H NMR (CDCl_3) δ (ppm): 3.94 (s, 3H), 4.70 (s, 2H), 7.43 (t, 1H, J = 8.1 Hz), 7.71 (dd, 1H, J = 8.1, 1.1 Hz), 7.96 (dd, 1H, J = 8.1, 1.2 Hz); signals imputable to the enol form (~10%) δ (ppm): 3.89 (s, 3H), 6.25 (bs, 1H, exchangeable), 6.72 (s, 1H), 7.62 (d, 1H, J = 8.1 Hz).

**Methyl 3-(2-bromo-6-nitrophenyl)-2-oxopropanoate (3e).** (76% yield from 2e) R_f = 0.56 (CH_2Cl_2); ^1^H NMR (CDCl_3) δ (ppm): 3.96 (s, 3H), 4.74 (s, 2H), 7.38 (t, 1H, J = 8.1 Hz), 7.91 (dd, 1H, J = 8.1, 1.3 Hz), 8.02 (dd, 1H, J = 8.1, 1.3 Hz); signals imputable to the enol form (~5%) δ (ppm): 3.90 (s, 3H), 6.71 (s, 1H), 7.84 (d, 1H, J = 8.1 Hz).

**Methyl 3-(4-bromo-2-nitrophenyl)-2-oxopropanoate (3f).** (78% yield from 2f) R_f = 0.27 (n-hexane/EtOAc 8:2); ^1^H NMR (CDCl_3) δ (ppm): 3.94 (s, 3H), 4.50 (s, 2H), 7.21 (d, 1H, J = 8.2 Hz), 7.77 (dd, 1H, J = 8.2, 2.0 Hz), 8.32 (d, 1H, J = 2.0 Hz); signals imputable to the enol form (~20%) δ (ppm): 3.91 (s, 3H), 6.72 (bs, 1H, exchangeable), 6.86 (s, 1H), 7.71 (dd, 1H, J = 8.6, 2.0 Hz), 8.04 (d, 1H, J = 2.0 Hz), 8.15 (d, 1H, J = 8.6 Hz).

**Methyl 3-(3-nitrobiphenyl-2-yl)-2-oxopropanoate (3g).** (76% yield from 2g) R_f = 0.24 (n-hexane/EtOAc 8:2); ^1^H NMR (CDCl_3) δ (ppm): 3.88 (s, 3H), 4.36 (s, 2H), 7.22-7.28 (m, 2H), 7.38-7.45 (m, 3H), 7.51 (t, 1H, J = 7.7 Hz), 7.59 (dd, 1H, J = 7.7, 1.8 Hz), 8.13 (dd, 1H, J = 7.9, 1.8 Hz); signals imputable to the enol form (~5%) δ (ppm): 3.80 (s, 3H), 5.94 (bs, 1H, exchangeable), 6.52 (s, 1H), 7.86 (dd, 1H, J = 8.0, 1.6 Hz).

**Methyl 3-(2-nitro-4-(tetrazol-5-yl)phenyl)-2-oxopropanoate (3k).** This product was synthesized from 2k by a slight modification of the general procedure reported above, consisting in the use of 8.0 equivalents of NaH (48% yield from 2k). R_f = 0.14 (CH_2Cl_2/MeOH 9:1); ^1^H NMR
(DMSO-$d_6$) $\delta$ (ppm): 3.80 (s, 3H), 4.71 (s, 2H), 8.34 (dd, 1H, $J = 8.5, 1.7$ Hz), 8.43 (d, 1H, $J = 8.4$ Hz), 8.57 (d, 1H, $J = 1.6$ Hz); signals imputable to the enol form (~ 40%) $\delta$ (ppm): 3.76 (s, 3H), 6.67 (s, 1H), 8.65 (dd, 1H, $J = 8.4, 1.8$ Hz), 8.74 (d, 1H, $J = 1.8$ Hz).

General procedure for the reductive cyclization leading to $N$-hydroxyindoles 4a-g. Ketoesters 3a-g (1.0 mmol) were dissolved in anhydrous DME (1.0 mL) and the resulting solution was added dropwise to a cooled (0 °C) solution of SnCl$_2$·2H$_2$O (2.2 mmol) in DME (1.0 mL) containing activated 4Å molecular sieves. The reaction mixture was stirred under nitrogen at RT until consumption of starting material (TLC), then it was diluted with water and extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography over iron-free silica gel$^4$ using the indicated eluant, to give the $N$-hydroxyindoles.

Methyl 1-hydroxy-1H-indole-2-carboxylate (4a).$^5$ (63% yield from 3a) $R_f = 0.33$ (CH$_2$Cl$_2$); $^1$H NMR (acetone-$d_6$) $\delta$ (ppm): 3.89 (s, 3H), 7.08 (d, 1H, $J = 0.9$ Hz), 7.13 (ddd, 1H, $J = 8.1, 7.0, 1.1$ Hz), 7.36 (ddd, 1H, $J = 8.1, 7.0, 1.1$ Hz), 7.53 (dq, 1H, $J = 8.4, 0.9$ Hz), 7.66 (dt, 1H, $J = 8.1, 1.0$ Hz), 10.36 (bs, 1H).

Methyl 1-hydroxy-4-methyl-1H-indole-2-carboxylate (4b). (56% yield from 3b) $R_f = 0.40$ (CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 2.53 (s, 3H), 3.97 (s, 3H), 6.91 (d, 1H, $J = 6.8$ Hz), 7.06 (d, 1H, $J = 0.7$ Hz), 7.25 (dd, 1H, $J = 8.4, 6.8$ Hz), 7.38 (d, 1H, $J = 8.4$ Hz), 10.18 (bs, 1H).

Methyl 1-hydroxy-4-trifluoromethyl-1H-indole-2-carboxylate (4c). (60% yield from 3c) $R_f = 0.19$ (n-hexane/CH$_2$Cl$_2$ 3:7); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 4.03 (s, 3H), 7.20 (qd, 1H, $J = 1.7, 1.0$ Hz), 7.40 (t, 1H, $J = 7.6$ Hz), 7.45 (d, 1H, $J = 6.6$ Hz), 7.72-7.76 (m, 1H), 10.40 (bs, 1H).

Methyl 4-chloro-1-hydroxy-1H-indole-2-carboxylate (4d). (72% yield from 3d) $R_f = 0.30$ (CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$) $\delta$ (ppm): 4.01 (s, 3H), 7.12-7.15 (m, 2H), 7.22-7.30 (m, 1H), 7.45 (d, 1H, $J = 8.2$ Hz), 10.35 (bs, 1H).
Methyl 4-bromo-1-hydroxy-1H-indole-2-carboxylate (4e). (58% yield from 3e) R_f = 0.37 (CH_2Cl_2); ^1H NMR (CDCl_3) δ (ppm): 4.02 (s, 3H), 7.08 (s, 1H), 7.20 (pseudo-t, 1H, J = 7.9 Hz), 7.32 (d, 1H, J = 7.3 Hz), 7.52 (d, 1H, J = 8.2 Hz), 10.33 (bs, 1H).

Methyl 6-bromo-1-hydroxy-1H-indole-2-carboxylate (4f). (41% yield from 3f) R_f = 0.19 (n-hexane/ethyl acetate 8:2); ^1H NMR (CDCl_3) δ (ppm): 3.99 (s, 3H), 7.00 (d, 1H, J = 0.9 Hz), 7.21 (dd, 1H, J = 8.7, 1.7 Hz), 7.49 (dd, 1H, J = 8.6, 0.7 Hz), 7.72 (dt, 1H, J = 1.5, 0.7 Hz), 10.22 (bs, 1H).

Methyl 1-hydroxy-4-phenyl-1H-indole-2-carboxylate (4g). (48% yield from 3g) R_f = 0.28 (n-hexane/ethyl acetate 7:3); ^1H NMR (CDCl_3) δ (ppm): 3.98 (s, 3H), 7.19 (d, 1H, J = 0.9 Hz), 7.20 (dd, 1H, J = 7.0, 1.1 Hz), 7.39-7.57 (m, 5H), 7.62-7.68 (m, 2H), 10.28 (bs, 1H). MS m/z 267 (M^+, 66), 253 (M^+–CH_2, 70), 190 (M^+–C_6H_5, 100).

Methyl 1-hydroxy-6-tetrazolyl-1H-indole-2-carboxylate (4k). Ketoester 3k (300 mg, 1.0 mmol) was dissolved in THF (2 mL) and the resulting solution was added to an aqueous solution (2 mL) of sodium hypophosphite monohydrate (0.5 g, 4.7 mmol). Then 15 mg of 10% palladium over charcoal was added and the resulting suspension was stirred at RT overnight. The mixture was concentrated, diluted with water and extracted with EtOAc. The organic phase was dried and evaporated to afford a crude residue that was purified by column chromatography over iron-free silica gel (CH_2Cl_2/MeOH 9:1 + 0.1% acetic acid, R_f = 0.15) to yield pure 4k (109 mg, 42% yield); ^1H NMR (DMSO-d_6) δ (ppm): 7.11 (d, 1H, J = 0.9 Hz), 7.79 (dd, 1H, J = 7.8, 1.5 Hz), 7.86 (d, 1H, J = 7.8 Hz), 8.17-8.19 (m, 1H).

Methyl 1-methoxy-6-phenyl-1H-indole-2-carboxylate (7). A solution of 4i (120 mg, 0.45 mmol) in anhydrous THF was treated with DBU (1.5 mL) and iodomethane (0.8 mL), and the resulting mixture was stirred at RT for 1 hour. An aqueous 1N HCl solution was added and the mixture was extracted with AcOEt. The organic phase was dried and evaporated to afford a crude residue that
was purified by column chromatography (n-hexane/ethyl acetate 8:2, R_f = 0.48) to give pure 7 (99 mg, 79% yield); ^1^H NMR (CDCl_3) δ (ppm): 3.96 (s, 3H), 4.24 (s, 3H), 7.13 (d, 1H, J = 0.7 Hz), 7.37-7.52 (m, 4H), 7.67-7.72 (m, 4H).

Preparation of final products 1a-g, 1k, 8, and 10h,i. General procedure: Methyl esters 4a-g, 4k, 7, and 9h,i (0.5 mmol) were dissolved in a 1:1 mixture of THF/methanol (5 mL) and treated with 1.5 mL of 2N aqueous solution of LiOH. The reaction was monitored by TLC and, after consumption of starting material, treated with 1N aqueous HCl and extracted with EtOAc. The organic phase was dried and evaporated to afford the desired carboxylic acid derivatives.

1-Hydroxy-1H-indole-2-carboxylic acid (1a).\(^5\) (98% yield from 4a) ^1^H NMR (DMSO-d_6) δ (ppm): 7.00 (d, 1H, J = 0.9 Hz), 7.08 (ddd, 1H, J = 8.1, 6.8, 1.1 Hz), 7.31 (ddd, 1H, J = 8.4, 6.8, 1.1 Hz), 7.43 (dq, 1H, J = 8.4, 1.1 Hz), 7.63 (dt, 1H, J = 8.1, 1.0 Hz), 11.73 (bs, 1H). ^13^C NMR (DMSO-d_6) δ (ppm): 106.17, 110.38, 121.52, 122.96, 123.14, 126.38, 136.92, 162.25. MS m/z 177 (M^+ 100), 161 159 (M^+–O, 28), 159 (M^+–H_2O, 13), 133 (M^+–CO_2, 5), 115 (M^+–H_2O –CO_2, 44). HPLC, t_R 7.1 min.

1-Hydroxy-4-methyl-1H-indole-2-carboxylic acid (1b). (79% yield from 4b) ^1^H NMR (DMSO-d_6) δ (ppm): 2.48 (s, 3H), 6.88 (d, 1H, J = 6.4 Hz), 7.02 (s, 1H), 7.15-7.27 (m, 2H), 11.37 (bs, 1H). ^13^C NMR (CD_3OD) δ (ppm): 18.14, 105.06, 108.14, 121.51, 122.83, 126.37, 126.55, 132.72, 137.66, 163.86. MS m/z 191 (M^+ 100), 175 (M^+–O, 6), 146 (M^+–CO_2 –H, 5), 129 (M^+–H_2O –CO_2, 19). HPLC, t_R 7.9 min.

1-Hydroxy-4-trifluoromethyl-1H-indole-2-carboxylic acid (1c). (83% yield from 4c) ^1^H NMR (DMSO-d_6) δ (ppm): 6.99 (qd, 1H, J = 1.7, 0.8 Hz), 7.43-7.53 (m, 2H), 7.75-7.80 (m, 1H). ^13^C NMR (acetone-d_6) δ (ppm): 103.60, 114.89, 117.91 (q, J = 3.0 Hz), 119.40 (q, J = 5.2 Hz), 123.27 (q, J = 34.8 Hz), 125.16, 125.51 (q, J = 260.9 Hz), 128.31, 136.96, 161.39. MS m/z 245 (M^+, 100), 229 (M^+–O, 9), 183 (M^+–H_2O –CO_2, 33). HPLC, t_R 8.8 min.
4-Chloro-1-hydroxy-1H-indole-2-carboxylic acid (1d). (99% yield from 4d) $^1$H NMR (DMSO-$d_6$) δ (ppm): 6.97 (s, 1H), 7.19 (dd, 1H, $J = 7.3, 0.9$ Hz), 7.31 (t, 1H, $J = 7.8$ Hz), 7.44 (d, 1H, $J = 8.2$ Hz). $^{13}$C NMR (acetone-$d_6$) δ (ppm): 103.64, 109.57, 121.14, 123.80, 126.67, 127.22, 127.82, 137.29, 161.65. MS m/z 211 (M$^+$, 100), 195 (M$^+$–O, 10), 149 (M$^+$–H$_2$O–CO$_2$, 13), 114 (M$^+$–H$_2$O–CO$_2$–Cl, 34). HPLC, $t_R$ 7.9 min.

4-Bromo-1-hydroxy-1H-indole-2-carboxylic acid (1e). (97% yield from 4e) $^1$H NMR (DMSO-$d_6$) δ (ppm): 6.88 (d, 1H, $J = 0.9$ Hz), 7.23 (t, 1H, $J = 7.8$ Hz), 7.35 (dd, 1H, $J = 7.4, 1.0$ Hz), 7.48 (dt, 1H, $J = 8.1, 1.0$ Hz). $^{13}$C NMR (acetone-$d_6$) δ (ppm): 105.06, 110.13, 116.53, 122.72, 124.29, 126.82, 127.38, 136.87, 161.61. MS m/z 257 ($^{81}$Br: M$^+$, 91), 255 ($^{79}$Br: M$^+$, 100), 241 ($^{81}$Br: M$^+$–O, 5), 239 ($^{79}$Br: M$^+$–O, 8), 114 (M$^+$–H$_2$O–CO$_2$–Br, 66). HPLC, $t_R$ 8.5 min.

6-Bromo-1-hydroxy-1H-indole-2-carboxylic acid (1f). (99% yield from 4f) $^1$H NMR (DMSO-$d_6$) δ (ppm): 7.03 (d, 1H, $J = 0.7$ Hz), 7.22 (dd, 1H, $J = 8.0, 1.7$ Hz), 7.59-7.63 (m, 2H). $^{13}$C NMR (acetone-$d_6$) δ (ppm): 106.35, 113.07, 119.37, 121.32, 124.83, 124.92, 127.42, 137.38, 161.67. MS m/z 257 ($^{81}$Br: M$^+$, 93), 255 ($^{79}$Br: M$^+$, 100), 241 ($^{81}$Br: M$^+$–O, 4), 239 ($^{79}$Br: M$^+$–O, 7), 114 (M$^+$–H$_2$O–CO$_2$–Br, 39). HPLC, $t_R$ 8.3 min.

1-Hydroxy-4-phenyl-1H-indole-2-carboxylic acid (1g). (89% yield from 4g) $^1$H NMR (DMSO-$d_6$) δ (ppm): 7.03 (d, 1H, $J = 0.7$ Hz), 7.19 (dd, 1H, $J = 6.6, 1.7$ Hz), 7.37–7.57 (m, 5H), 7.64–7.69 (m, 2H). $^{13}$C NMR (acetone-$d_6$) δ (ppm): 105.31, 109.61, 120.50, 121.17, 126.43, 126.73, 128.29, 129.37 (2C), 129.55 (2C), 136.65, 137.43, 140.67, 162.01. MS m/z 253 (M$^+$, 100), 237 (M$^+$–O, 8), 191 (M$^+$–H$_2$O–CO$_2$, 25), 190 (M$^+$–H$_2$O–CO$_2$–H, 62), 165 (M$^+$–H$_2$O–CO$_2$–C$_2$H$_2$, 62). HPLC, $t_R$ 8.9 min.

1-Hydroxy-6-tetrazolyl-1H-indole-2-carboxylic acid (1k). (97% yield from 4k) $^1$H NMR (DMSO-$d_6$) δ (ppm): 7.11 (d, 1H, $J = 0.9$ Hz), 7.79 (dd, 1H, $J = 7.8, 1.5$ Hz), 7.86 (d, 1H, $J = 7.8$ Hz), 8.17–8.19 (m, 1H). $^{13}$C NMR (DMSO-$d_6$) δ (ppm): 104.63, 108.58, 118.82, 122.66, 123.28, 128.85, 135.40, 160.84. HPLC, $t_R$ 1.4 min.

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1-Methoxy-6-phenyl-1H-indole-2-carboxylic acid (8). (99% yield from 7) $^1$H NMR (CDCl$_3$) δ (ppm): 4.26 (s, 3H), 7.31 (s, 1H), 7.39-7.53 (m, 4H), 7.67-7.76 (m, 4H). $^{13}$C NMR (CDCl$_3$) δ (ppm): 66.40 (OMe), 107.66, 109.35, 121.19, 121.86, 123.37, 124.59, 127.62 (2C), 128.11, 128.98 (2C), 136.43, 140.16, 141.38, 164.60. MS m/z 267 (M$^+$, 50), 253 (M$^+$ –CH$_2$, 30), 237 (M$^+$ –O –CH$_2$, 9), 191 (M$^+$ –CH$_2$ –H$_2$O –CO$_2$, 40), 190 (M$^+$ –CH$_2$ –H$_2$O –CO$_2$ –H, 100), 165 (M$^+$ –CH$_2$ –H$_2$O –CO$_2$ –C$_2$H$_2$, 21). HPLC, $t_R$ = 8.6 min (purity = 93%, major impurity accounting for >6% of residual peak area identified as 10i).

5-Phenyl-1H-indole-2-carboxylic acid (10h). (99% yield from 9h) $^1$H NMR (acetone-$d_6$) δ (ppm): 7.27 (d, 1H, $J = 2.2$ Hz), 7.32-7.35 (m, 1H), 7.42-7.50 (m, 2H), 7.62-7.72 (m, 4H), 7.95-7.97 (m, 1H), 10.93 (bs, 1H). $^{13}$C NMR (acetone-$d_6$) δ (ppm): 109.12, 113.58, 121.03, 125.29, 127.29, 127.73, 127.76 (2C), 128.93, 129.55 (2C), 134.43, 137.81, 142.75, 162.83. MS m/z 237 (M$^+$, 100), 191 (M$^+$ –HCOOH, 10), 190 (M$^+$ –HCOOH –H, 26), 165 (M$^+$ –HCOOH –C$_2$H$_2$, 11). HPLC, $t_R$ 8.2 min.

6-Phenyl-1H-indole-2-carboxylic acid (10i). (99% yield from 9i) $^1$H NMR (acetone-$d_6$) δ (ppm): 7.23 (dd, 1H, $J = 2.2$, 0.9 Hz), 7.34-7.52 (m, 4H), 7.67-7.80 (m, 4H), 10.94 (bs, 1H). $^{13}$C NMR (acetone-$d_6$) δ (ppm): 108.70, 111.19, 121.00, 123.38, 126.10, 127.80, 127.89 (2C), 129.62 (2C), 129.65, 138.76, 142.60, 162.60. MS m/z 237 (M$^+$, 38), 191 (M$^+$ –HCOOH, 40), 190 (M$^+$ –HCOOH –H, 100). HPLC, $t_R$ = 9.2 min.
Figure S1. Analysis of the MD simulation of the LDH-Ij complex. Total energy (kcal/mol) of the system plotted vs time (A) and RMSD in angstrom of the $\alpha$ carbon of the protein from the starting model structure during the simulation (B) are reported.
Table S1. Hydrogen Bonds Analysis of the LDH-1j interactions during the last 5.5 ns of MD Simulation.α

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<td>LIG@O3</td>
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<td>T248@OG1</td>
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</tr>
</tbody>
</table>

α WAT = water, LIG = ligand 1j.
REFERENCES.


