

## SUPPORTING INFORMATION

### ***Onchocerca volvulus* molting inhibitors identified through scaffold hopping**

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## EXPERIMENTAL PROCEDURES

**Chemistry.** All reactions were performed under nitrogen atmosphere, unless otherwise specified.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DRX-600 equipped with a 5 mm DCH cryoprobe or Varian Inova-400.

General procedure for the syntheses of compounds **2a-c**. The acyl chloride/chloroformate (1.2 eq) was added dropwise to a solution of 4-(4-chlorophenoxy)aniline **5** (1.0 eq) and DIPEA (3.0 eq) in DMF, and the reaction was stirred for 0.5 h. The mixture was diluted with  $\text{H}_2\text{O}$ , and extracted with EtOAc. The organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography.

*N*-(4-(4-Chlorophenoxy)phenyl)benzamide (**2a**). Yield: 37%.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.93 (d,  $J$  = 8.1 Hz, 2H), 7.02 (d,  $J$  = 8.2 Hz, 2H), 7.28 (d,  $J$  = 8.1 Hz, 2H), 7.50 (t,  $J$  = 7.4 Hz, 2H), 7.56 (t,  $J$  = 7.3 Hz, 1H), 7.62 (d,  $J$  = 8.2 Hz, 2H), 7.82 (s, 1H), 7.87 (d,  $J$  = 7.7 Hz, 2H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  119.8, 119.9, 122.2, 127.1, 128.3, 129.0, 129.9, 132.1, 133.9, 134.9, 153.5, 156.3, 165.8. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{15}\text{ClNO}_2$ , 324.0791; found, 324.0790.

*N*-(4-(4-Chlorophenoxy)phenyl)-2-phenylacetamide (**2b**). Yield: 51%.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  3.75 (s, 2H), 6.88 (d,  $J$  = 8.3 Hz, 2H), 6.93 (d,  $J$  = 8.4 Hz, 2H), 7.05 (s, 1H), 7.26 (d, 2H), 7.32 – 7.44 (m, 7H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  44.9, 119.7, 119.8, 121.8, 127.9, 128.2, 129.5, 129.7, 129.8, 133.6, 134.5, 153.3, 156.4, 169.2. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{18}\text{ClNO}_2$ , 338.0948; found, 338.0949.

Phenyl 4-(4-chlorophenoxy)phenylcarbamate (**2c**). Yield: 52%.  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.92 (dt,  $J$  = 3.1, 10.0 Hz, 2H), 6.97 – 7.02 (m, 2H), 7.17 – 7.21 (m, 2H), 7.22 – 7.30 (m, 3H), 7.40 (td,  $J$  = 1.9, 7.6 Hz, 2H), 7.43 (d,  $J$  = 8.1 Hz, 2H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  115.4, 119.7, 120.1, 120.7, 121.7, 125.9, 128.2, 129.6, 129.8, 133.4, 150.7, 153.0, 156.4. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{15}\text{ClNO}_3$ , 340.0740; found, 340.0742.

General procedure for the syntheses of compounds **2d-k**. The aryl/alkyl isocyanate (1.3 – 1.5 eq) was added dropwise to a solution of 4-(4-chlorophenoxy)aniline (1.0 eq) and DIPEA (3.0 eq) in DMF, and the reaction was stirred for 3 h at rt. The mixture was concentrated *in vacuo* and the desired urea derivative was either purified by silica column chromatography or recrystallized in EtOH.

1-(4-(4-Chlorophenoxy)phenyl)-3-phenylurea (**2d**). Yield: 60%.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  6.94 – 6.99 (m, 3H), 6.99 – 7.03 (m, 2H), 7.27 (t,  $J$  = 7.9 Hz, 2H), 7.38 – 7.42 (m, 2H), 7.43 – 7.47 (m, 2H), 7.47 – 7.51 (m, 2H), 8.64 (s, 1H), 8.69 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO}$ )  $\delta$  118.2, 119.1, 119.9, 120.0, 121.8, 126.4, 128.8, 129.7, 136.1, 139.7, 150.1, 152.6, 156.7. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2$ , 339.0900; found, 339.0903.

1-(4-(4-Chlorophenoxy)phenyl)-3-(4-chlorophenyl)urea (**2e**). Yield: 65%.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  6.97 (d,  $J$  = 8.7 Hz, 2H), 7.01 (d,  $J$  = 8.7 Hz, 2H), 7.32 (d,  $J$  = 8.6 Hz, 2H), 7.40 (d,  $J$  = 8.7 Hz, 2H), 7.44 – 7.53 (m, 4H), 8.74 (s, 1H), 8.81 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO}$ )  $\delta$  119.2, 119.7, 120.0, 120.1, 125.3, 126.4, 128.6, 129.7, 135.9, 138.7, 150.3, 152.5, 156.6. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{15}\text{Cl}_2\text{N}_2\text{O}_2$ , 373.0505; found, 373.0506.

1-(4-(4-Chlorophenoxy)phenyl)-3-(4-cyanophenyl)urea (**2f**). Yield: 36%.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  6.94 – 7.00 (m, 2H), 7.00 – 7.08 (m, 2H), 7.36 – 7.45 (m, 2H), 7.45 – 7.53 (m, 2H), 7.59 – 7.68 (m, 2H), 7.69 – 7.80 (m, 2H), 8.89 (s, 1H), 9.19 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz,  $\text{DMSO}$ )  $\delta$  103.2, 118.0, 119.3, 120.0, 120.4, 126.5, 129.8, 133.3, 133.4, 135.5, 144.2, 150.7, 152.1, 156.5. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{15}\text{ClN}_3\text{O}_2$ , 364.0847; found, 364.0858.

1-(4-(4-Chlorophenoxy)phenyl)-3-(2,4-dichlorophenyl)urea (**2g**). Yield: 39%.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  6.96 – 7.00 (m, 2H), 7.01 – 7.04 (m, 2H), 7.38 (dd,  $J$  = 2.4, 9.0 Hz, 1H), 7.41 (m, 2H), 7.47

– 7.51 (m, 2H), 7.62 (d,  $J = 2.5$  Hz, 1H), 8.20 (d,  $J = 9.0$  Hz, 1H), 8.37 (s, 1H), 9.47 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  119.3, 120.0, 120.0, 122.0, 122.6, 126.0, 126.5, 127.6, 128.6, 129.8, 135.2, 135.6, 150.6, 152.0, 156.5. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{14}\text{Cl}_3\text{N}_2\text{O}_2$ , 407.0115; found, 407.0116.

1-(4-Chlorophenethyl)-3-(4-(4-chlorophenoxy)phenyl)urea (**2h**). Yield: 44%.  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  1.17 (t,  $J = 7.1$  Hz, 2H), 2.74 (t,  $J = 7.0$  Hz, 2H), 6.09 (t,  $J = 5.6$  Hz, 1H), 6.93 – 6.95 (m, 4H), 7.27 (d,  $J = 8.2$  Hz, 2H), 7.34 – 7.43 (m, 6H), 8.51 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  35.1, 40.4, 118.9, 119.2, 120.0, 126.2, 128.3, 129.7, 130.6, 130.7, 137.0, 138.6, 149.4, 155.1, 156.9. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_2$ , 401.0818; found, 401.0821.

4-Chloro-*N*-((4-(4-chlorophenoxy)phenyl)carbamoyl)benzenesulfonamide (**2i**). Yield: 32%.  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  6.94 – 6.97 (m, 2H), 6.97 – 7.00 (m, 2H), 7.35 – 7.38 (m, 2H), 7.38 – 7.42 (m, 2H), 7.71 – 7.74 (m, 2H), 7.96 – 7.99 (m, 2H), 9.04 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  119.4, 119.8, 121.0, 126.7, 129.2, 129.4, 129.8, 134.1, 138.2, 138.8, 149.4, 151.4, 156.3. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{19}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$ , 437.0124; found, 437.0126.

1-(4-(4-Chlorophenoxy)phenyl)-3-(3,5-dimethylisoxazol-4-yl)urea (**2j**). Yield: 38%.  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  2.11 (s, 3H), 2.28 (s, 3H), 6.95 (d,  $J = 8.9$  Hz, 2H), 6.99 (d,  $J = 8.9$  Hz, 2H), 7.39 (d,  $J = 8.8$  Hz, 2H), 7.48 (d,  $J = 8.8$  Hz, 2H), 7.69 (s, 1H), 8.84 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  9.5, 10.7, 114.7, 119.1, 119.9, 120.0, 126.4, 129.7, 136.3, 150.1, 153.5, 156.7, 158.0, 162.5. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{18}\text{H}_{17}\text{ClN}_3\text{O}_3$ , 358.0958; found, 358.0959.

1-((3*s*,5*s*,7*s*)-Adamantan-1-yl)-3-(4-(4-chlorophenoxy)phenyl)urea (**2k**). Yield: 32%.  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  1.63 (m, 5H), 1.82 (m, 2H), 1.92 (m, 5H), 2.02 (m, 3H), 5.84 (s, 1H), 6.92 (d,  $J = 2.1$  Hz, 2H), 6.93 (d,  $J = 2.0$  Hz, 2H), 7.34 – 7.39 (m, 4H), 8.29 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  28.9, 36.0, 41.7, 49.8, 118.9, 118.9, 120.0, 126.2, 129.7, 137.2, 149.2, 154.0, 156.9. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{26}\text{ClN}_2\text{O}_2$ , 397.1677; found, 397.1676.

1-(4-(4-Chlorophenoxy)phenyl)-3-(4-hydroxy-5-oxocyclohepta-1,3,6-trien-1-yl)urea (**3a**). 4-Nitrophenyl (4-(4-chlorophenoxy)phenyl)carbamate (1.0 eq) and 5-aminotropolone **6** (1.0 eq, synthesized as described previously<sup>1</sup>) were added to dry THF in a microwave reaction tube with a stir bar. The vial was placed in the microwave heater and heated to 95 °C with stirring using the following settings: max. pressure 250 psi, 300 watts, and medium stirring for 2.5 h. THF was removed under reduced pressure, and the crude product was purified by silica gel column chromatography. Yield: 37%.  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  6.95 – 6.99 (m, 2H), 6.99 – 7.03 (m, 2H), 7.20 – 7.25 (m, 2H), 7.37 – 7.43 (m, 2H), 7.45 – 7.51 (m, 2H), 7.56 – 7.61 (m, 2H), 8.85 (s, 1H), 8.91 (s, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  115.8, 119.3, 119.9, 120.2, 125.1, 126.2, 126.5, 127.7, 129.8, 135.7, 139.8, 150.5, 152.6, 156.6, 168.8. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{16}\text{ClN}_2\text{O}_4$ , 383.0793; found, 383.0798.

Compounds **3b-e** were prepared as previously described.<sup>1</sup>

*N*-(4-Hydroxy-5-oxocyclohepta-1,3,6-trien-1-yl)-4-phenoxybenzamide (**3f**). 4-Phenoxybenzoic acid (0.60 mmol), EDC (0.72 mmol), Cl-HOBt (0.72 mmol), and anhydrous DMF (7 mL) were added to a round bottom flask and stirred at room temperature under an inert atmosphere. After 1 h, 5-aminotropolone<sup>1</sup> (0.6 mmol) dissolved in 1 mL anhydrous DMF was added to the stirring reaction mixture. After 18 h, the mixture was concentrated under reduced pressure and purified via silica column chromatography to give **3f** in 55% yield.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.32 – 7.12 (m, 10H), 7.52 (t,  $J = 8$  Hz, 2H), 8.08 (d,  $J = 8$  Hz, 2H).  $^{13}\text{C}$  NMR (150 MHz, DMSO)  $\delta$  118.2, 120.9, 124.6, 125.7, 129.1, 131.2, 133.0, 155.9, 156.6, 162.4, 163.2, 169.1, 169.2. HRMS-ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{16}\text{NO}_4$ , 334.1074; found, 334.1079.

General procedure for the syntheses of oxadiazoles **4a-b**. A solution of (Z)-4-chloro-*N*-hydroxybenzimidamide **7** (1.0 eq, prepared as previously reported<sup>2</sup>), appropriate carboxylic acid (1.0 eq), DIPEA (3.0 eq) and HBTU (1.1 eq) in DMF was heated under reflux for 3 h and then partitioned between H<sub>2</sub>O and EtOAc. The organic phase was separated and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The crude oxadiazole was recrystallized in EtOH.

5-(4-(4-Chlorophenoxy)phenyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**4a**). Yield: 38%. <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.16 – 7.29 (m, 4H), 7.48 – 7.59 (m, 2H), 7.62 – 7.73 (m, 2H), 8.05 – 8.15 (m, 2H), 8.15 – 8.26 (m, 2H). <sup>13</sup>C NMR (151 MHz, DMSO)  $\delta$  39.5, 109.5, 118.0, 118.3, 122.0, 125.0, 128.9, 129.5, 130.3, 130.4, 136.4, 153.7, 161.1, 167.4, 175.1. HRMS-ESI (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>13</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>, 383.0349; found, 383.0350.

5-([1,1'-Biphenyl]-4-yl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**4b**). Yield: 40%. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.43 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.53 (m, 4H), 7.65 – 7.69 (m, 2H), 7.77 – 7.81 (m, 2H), 8.12 – 8.17 (m, 2H), 8.26 – 8.30 (m, 2H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  123.0, 125.7, 127.4, 127.9, 128.5, 128.8, 129.0, 129.2, 129.3, 137.5, 139.8, 145.8, 168.4, 175.9. HRMS-ESI (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>14</sub>ClN<sub>2</sub>O, 333.0795; found, 333.0798.

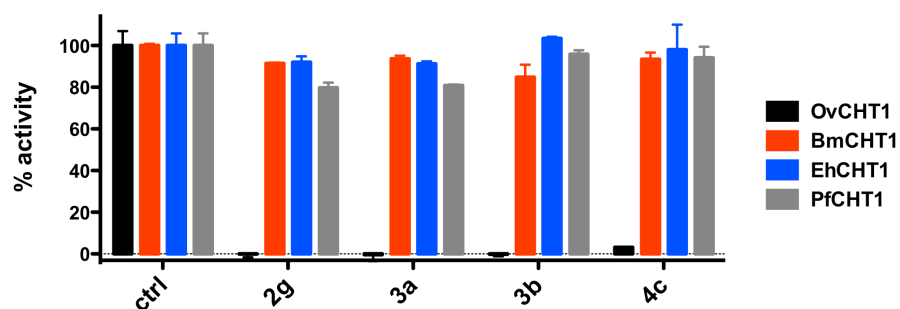
**Molecular Docking.** The PDB file of the homology model of OvCHT1 structure was provided by Dr. Aldo Segura-Cabrera.<sup>3</sup> The pdbqt files for OvCHT1 and the ligands were generated using AutoDock Tools (version Nov 5, 2014).<sup>4</sup> The box was set to 21.75 × 21.75 × 21.75 nm and centered at xyz-coordinates (-8.88, 0.00, 17.99). The ligands were docked into OvCHT1 using AutoDock Vina (version 1.1.2) using an exhaustiveness parameter of 8.

The procedures for the evaluation of **mitochondrial uncoupling** and *O. volvulus* **L3 molting** were the same as described previously.<sup>5</sup>

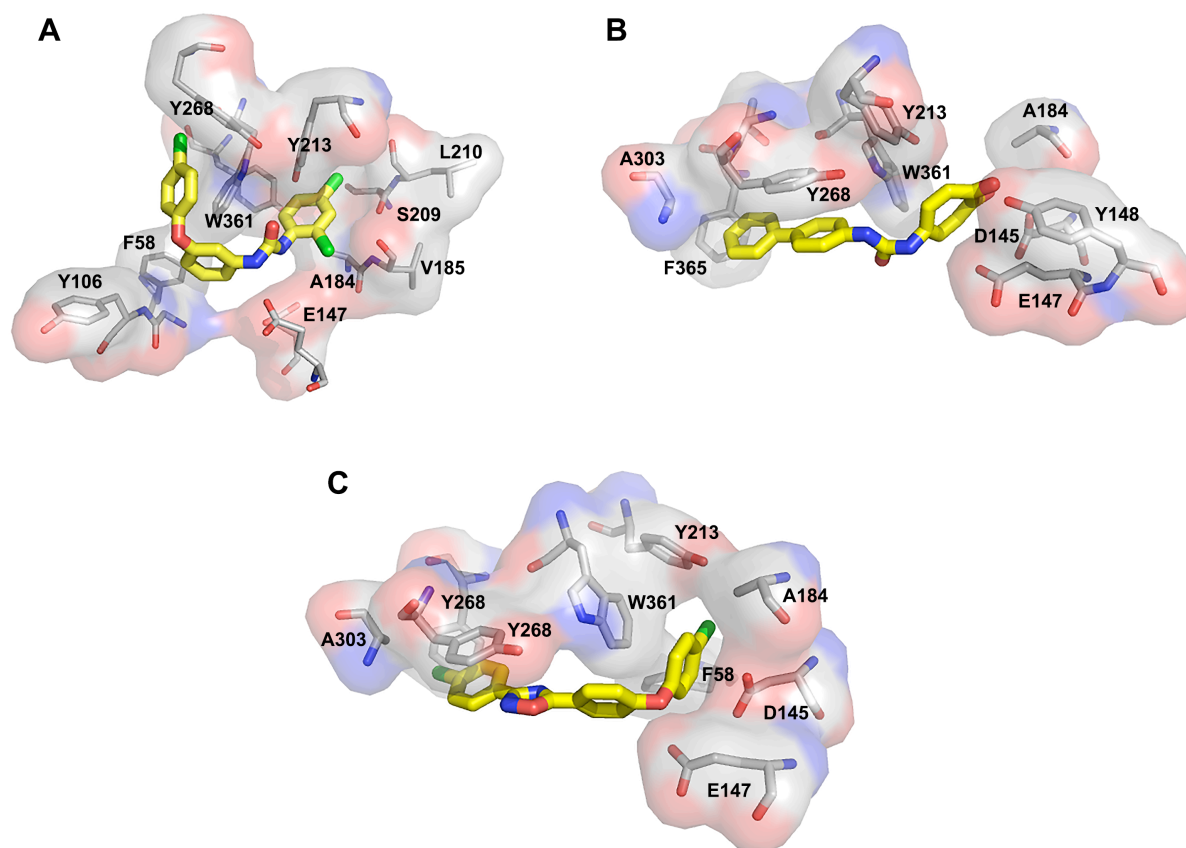
**Bioaccumulation in *C. elegans*.** Sample preparation and analysis of worm homogenates were carried out as reported previously.<sup>5</sup> Mass spectrometry acquisition was performed in the positive or negative electrospray ionization mode with the following parameters: capillary voltage = 3.5 kV, nebulizer pressure = 20 psig, drying gas flow = 7 L/min, and gas temperature = 350 °C. Worm homogenate samples were analyzed on a ZORBAX SB-C18 (1 × 150 mm, 3.5  $\mu$ m, Agilent Technologies, Santa Clara, CA, USA). The mobile phase consisted of elution at 0.10 mL/min starting with 70% A/30 % B for 1 min, followed by a 5-min linear gradient to 100% B, and then 100% B for 12 min [(+)-ESI: A = 0.1% TFA in water, B = 0.1% TFA in acetonitrile; (-)-ESI: A = water, B = acetonitrile]. The mass filters used for extracting ion chromatograms were as follows: *m/z* = 404.900 – 405.100 for **2g**, *m/z* = 380.900 – 381.200 for **3a**, *m/z* = 382.900 – 383.200 for **4a**. Identification of compounds in the worm homogenates was confirmed by comparison of HPLC retention time and mass spectrum with those of authentic synthetic standards.

**Cell Viability.** Adherent human epithelial cells (HEK 293T/17, 1 × 10<sup>4</sup> cells, ATCC CRL-11268) were seeded into a 96-well plate and incubated at 37 °C for 48 h. Cells were then treated with the compounds (10  $\mu$ M) and MTS assay was performed at 24 h postincubation using the CellTiter 96<sup>®</sup> AQueous Non-Radioactive Cell Proliferation Assay (Promega, Madison, WI). The cells were incubated at 37 °C for 1 h and the absorbance at 490 nm was measured using a SpectraMaxM2e microplate reader (Molecular Devices, Sunnyvale, CA).

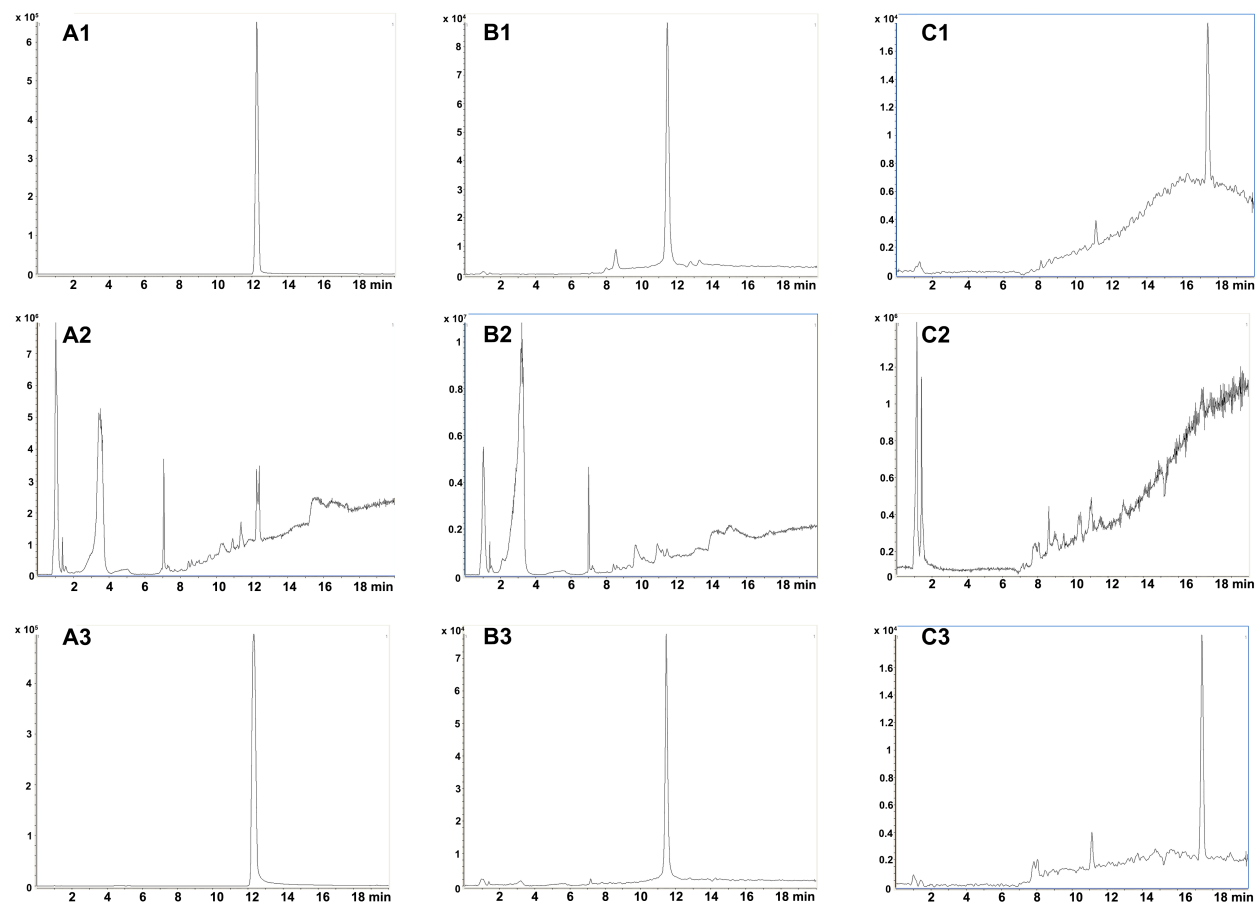
## SUPPLEMENTARY FIGURES



**Figure S1.** Activity of chitinases from different species in the presence of inhibitors (each at 10  $\mu$ M final concentration) relative to control (0.5% DMSO in water).



**Figure S2.** Lowest energy poses of compounds (A) **2g**, (B) **3b**, and (C) **4a** docked into OvCHT1 using the program AutoDock Vina. Color scheme: oxygens in red, nitrogens in blue, carbons in yellow (compounds **2g**, **3b**, and **4a**) or gray (OvCHT1)



**Figure S3.** Bioaccumulation in *C. elegans*. Late-stage L4 worms were incubated with 10  $\mu$ M of compound **2g**, **3a**, or **4a** for 6 h. (A1) standard **2g**; (A2) LC trace of worm lysate after incubation with **2g**; (A3) compound **2g** in worm lysate, (-)-EIC (extracted ion chromatogram) at  $m/z = 404.900 - 405.100$  a.m.u.; (B1) standard **3a**; (B2) LC trace of worm lysate after incubation with **3a**; (B3) compound **3a** in worm lysate, (-)-EIC at  $m/z = 380.900 - 381.200$  a.m.u.; (C1) standard **4a**; (C2) LC trace of worm lysate after incubation with **4a**; (C3) compound **4a** in worm lysate, (+)-EIC at  $m/z = 382.900 - 383.200$  a.m.u.

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