

# New synthetic and biological evaluation of uniflorine A derivatives: towards specific insect trehalase inhibitors

**Giampiero D'Adamio,<sup>#[a]</sup> Antonella Sgambato,<sup>#[b]</sup> Matilde Forcella,<sup>#[b]</sup> Silvia Caccia,<sup>#[c]</sup> Camilla Parmeggiani,<sup>[a][d]</sup> Morena Casartelli,<sup>[c]</sup> Paolo Parenti,<sup>[e]</sup> Davide Bini,<sup>[b]</sup> Laura Cipolla,<sup>[b]</sup> Paola Fusi<sup>\*[b]</sup> and Francesca Cardona<sup>\*[a]</sup>**

[a] Dipartimento di Chimica “Ugo Schiff”, University of Florence, Via della Lastruccia 3-13, 50019 Sesto Fiorentino (FI), Italy.

E-mail: [francesca.cardona@unifi.it](mailto:francesca.cardona@unifi.it)

[b] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Piazza della Scienza 2, 20126 Milano, Italy.

E-mail: [paola.fusi@unimib.it](mailto:paola.fusi@unimib.it)

[c] Department of Biosciences, University of Milano, Via Celoria 26, 20133 Milano, Italy

[d] CNR-INO, U.O.S. Sesto Fiorentino and LENS, via Nello Carrara 1, 50019 Sesto Fiorentino (FI), Italy.

[e] Dipartimento di Scienze dell'Ambiente e del Territorio e di Scienze della Terra, University of Milano-Bicocca, Piazza della Scienza 1, 20126 Milano, Italy.

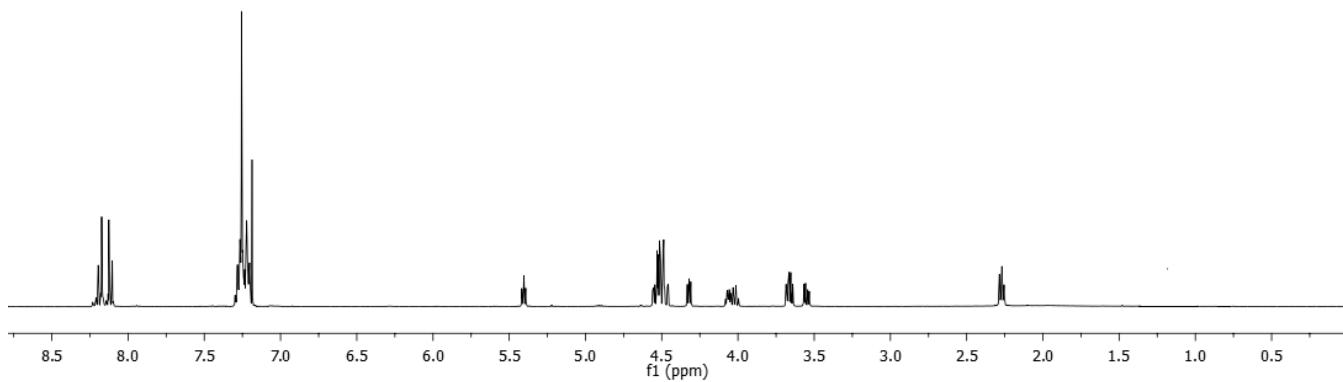
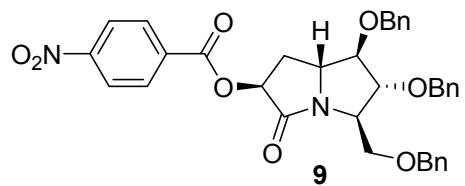
# These authors contributed equally to this work.

## Supporting Information

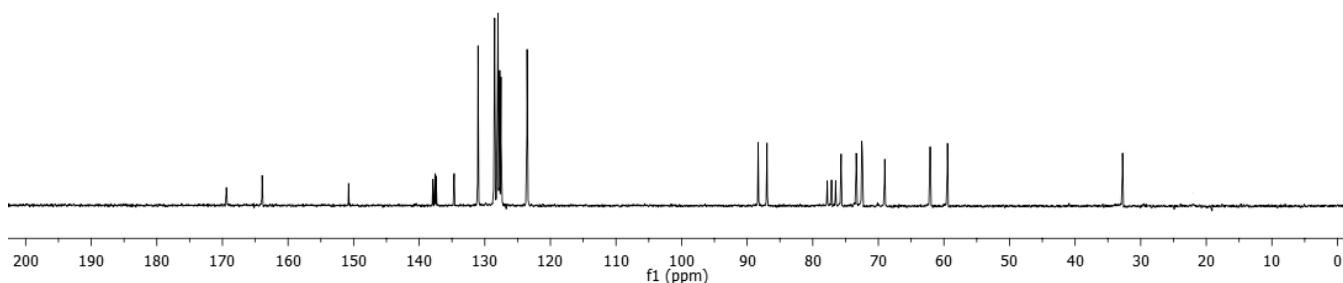
## Table of Contents

---

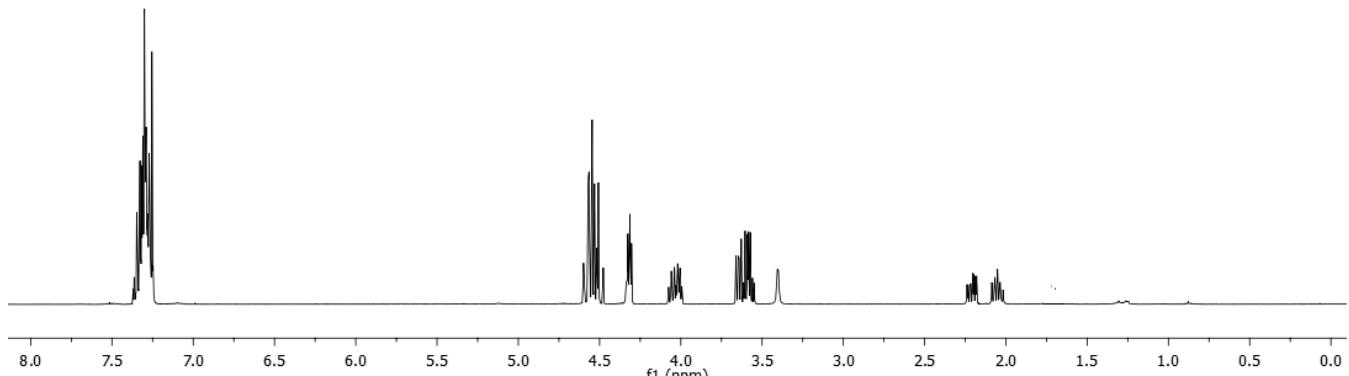
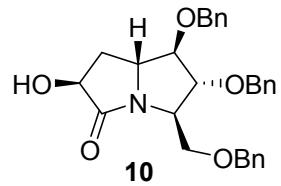
Figure S1. $^1\text{H}$ -NMR Spectrum of compound <b>9</b> .	S3
Figure S2. $^{13}\text{C}$ -NMR Spectrum of compound <b>9</b> .	S3
Figure S3. $^1\text{H}$ -NMR Spectrum of compound <b>10</b> .	S4
Figure S4. $^{13}\text{C}$ -NMR Spectrum of compound <b>10</b> .	S4
Figure S5. $^1\text{H}$ -NMR Spectrum of compound <b>11</b> .	S5
Figure S6. $^{13}\text{C}$ -NMR Spectrum of compound <b>11</b> .	S5
Figure S7. $^1\text{H}$ -NMR Spectrum of compound <b>6</b> .	S6
Figure S8. $^{13}\text{C}$ -NMR Spectrum of compound <b>6</b> .	S6
Figure S9. Inhibition kinetics of midge trehalase in the presence of compound <b>4</b> .	S7
Figure S10. Inhibition kinetics of midge trehalase in the presence of compound <b>5</b> .	S8
Figure S11. Inhibition kinetics of midge trehalase in the presence of compound <b>6</b> .	S9
Figure S12. Inhibition kinetics of midge trehalase in the presence of compound <b>7</b> .	S9
Figure S13. Bioassay on <i>S. littoralis</i> larvae.	S10



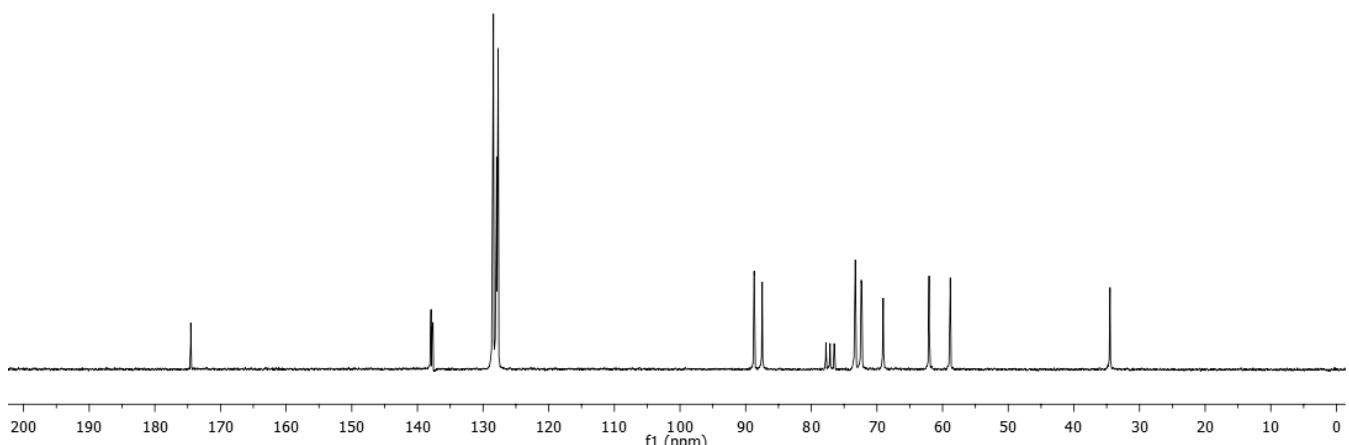
**Figure S1.**  $^1\text{H}$ -NMR spectrum of compound 9 (400 MHz,  $\text{CDCl}_3$ ).



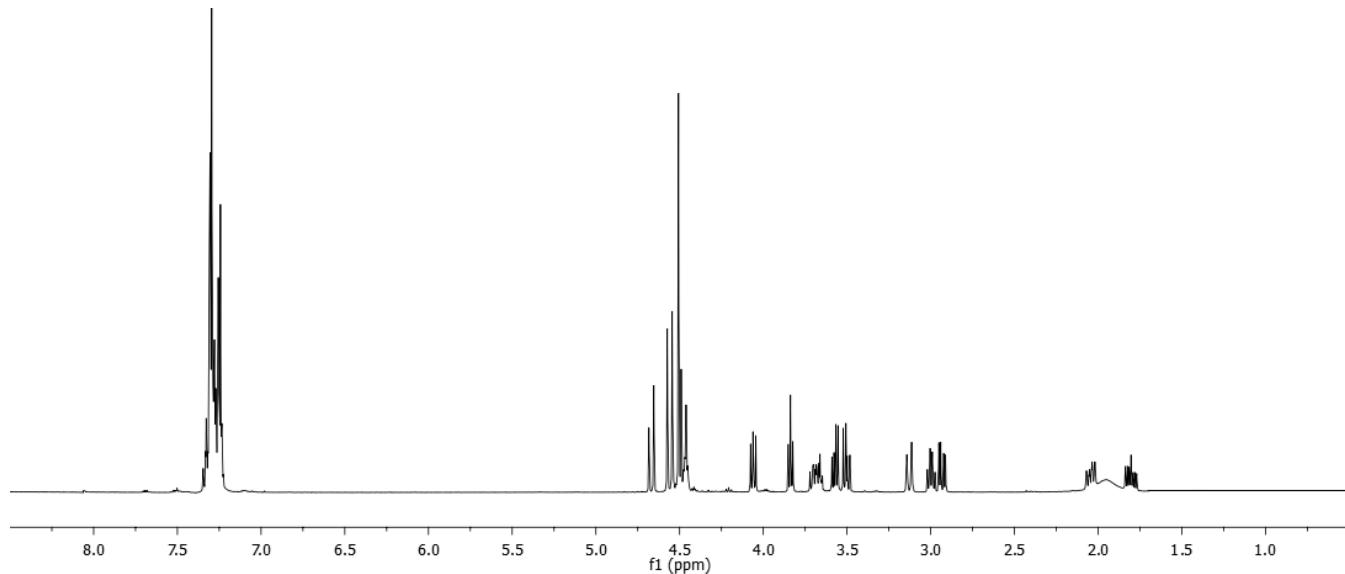
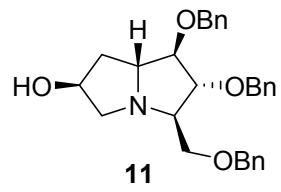
**Figure S2.**  $^{13}\text{C}$ -NMR spectrum of compound 9 (50 MHz,  $\text{CDCl}_3$ ).



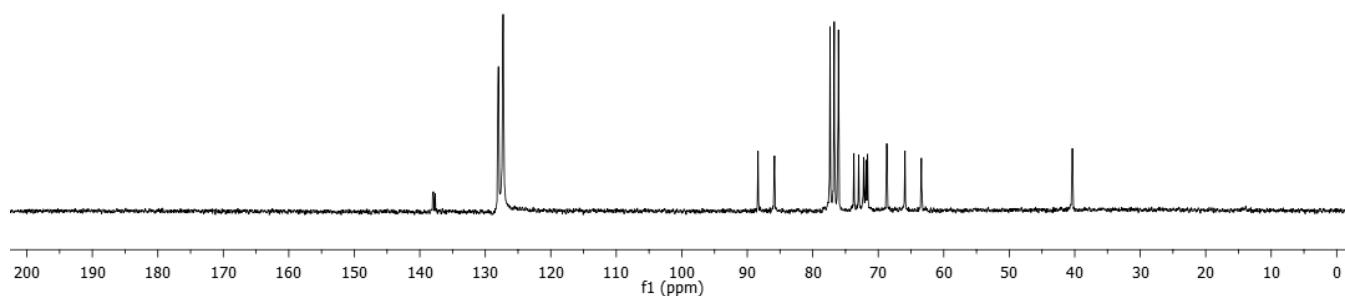
**Figure S3.**  $^1\text{H}$ -NMR spectrum of compound 10 (400 MHz,  $\text{CDCl}_3$ ).



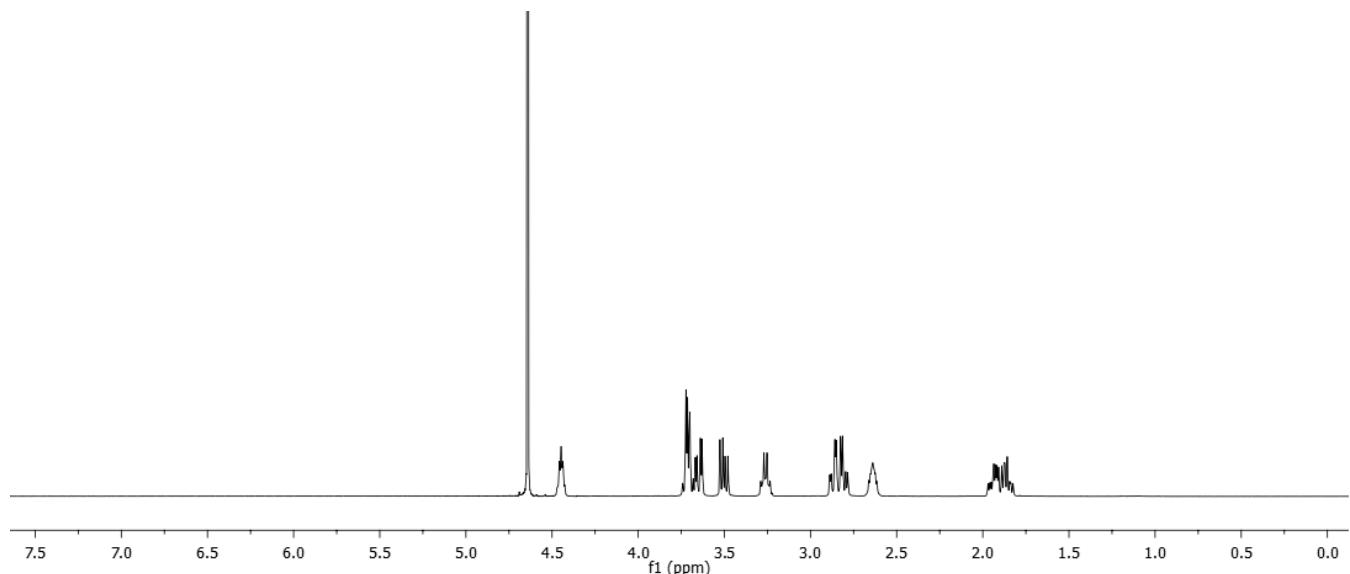
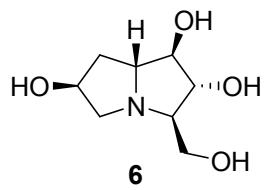
**Figure S4.**  $^{13}\text{C}$ -NMR spectrum of compound 10 (50 MHz,  $\text{CDCl}_3$ ).



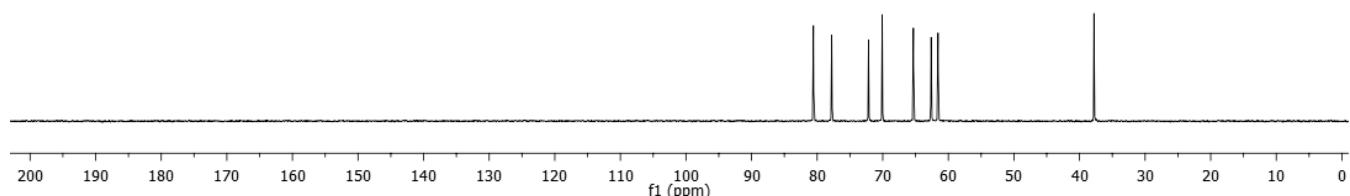
**Figure S5.**  $^1\text{H}$ -NMR spectrum of compound 11 (400 MHz,  $\text{CDCl}_3$ ).



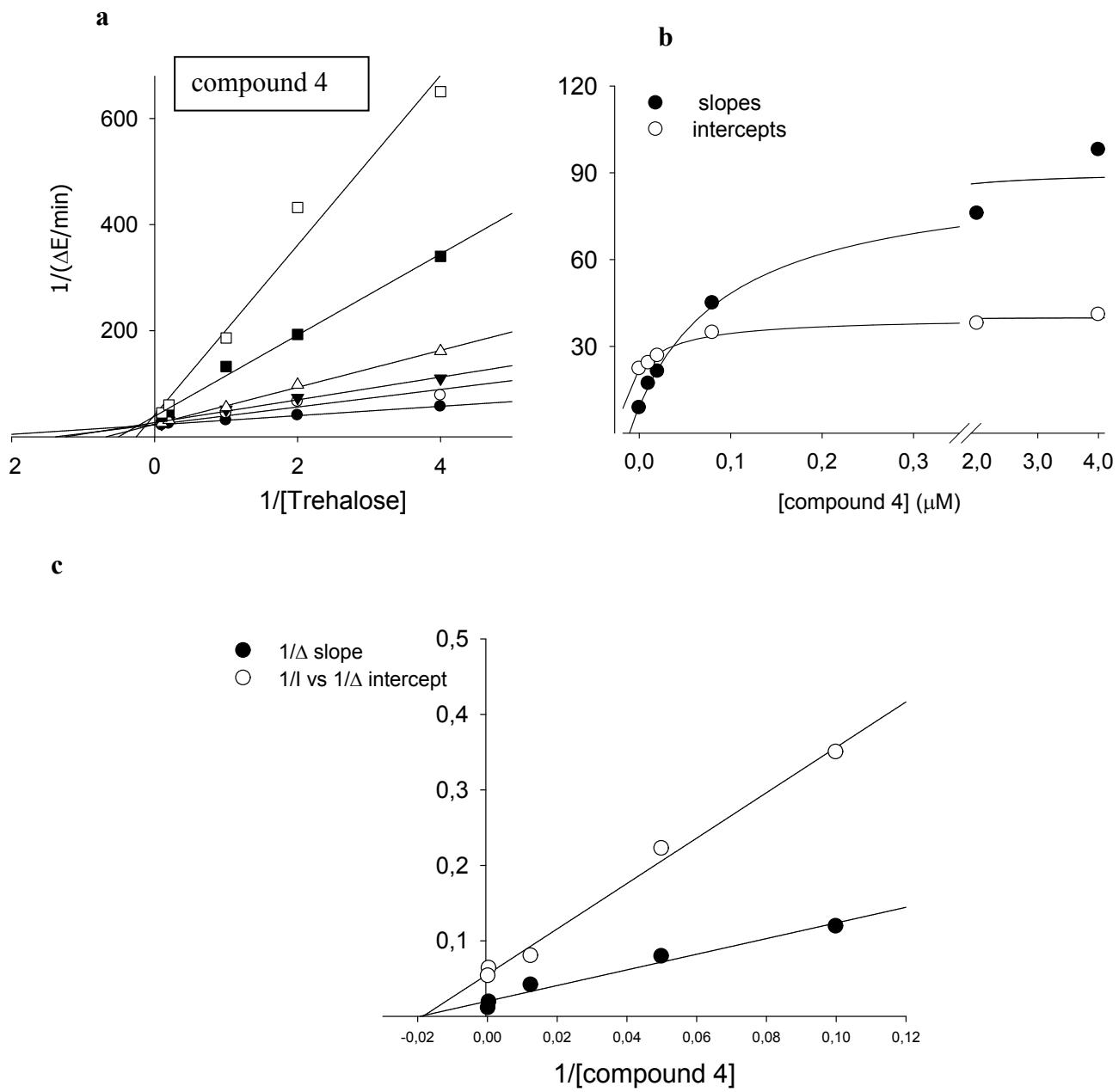
**Figure S6.**  $^{13}\text{C}$ -NMR spectrum of compound 11 (50 MHz,  $\text{CDCl}_3$ ).



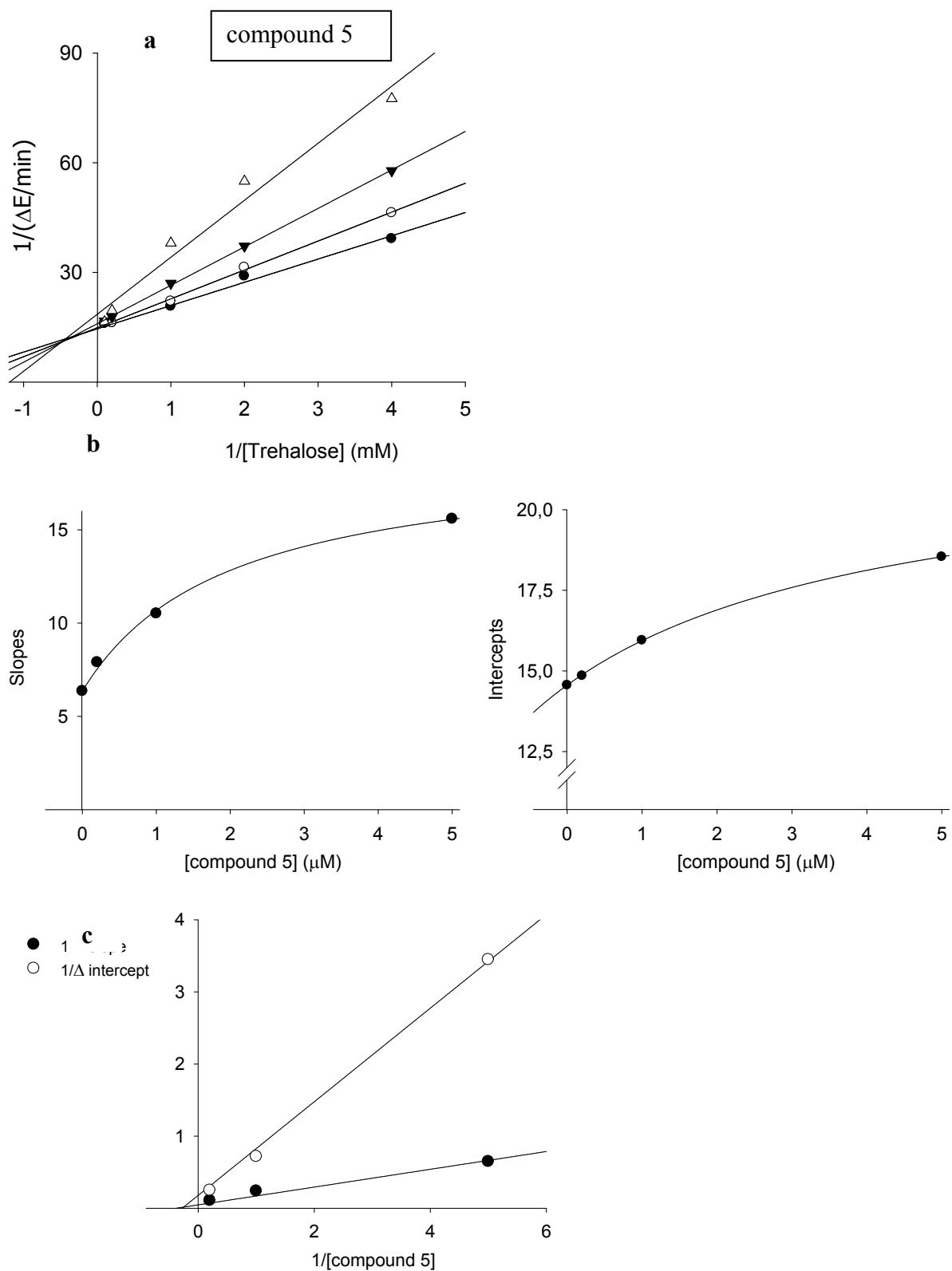
**Figure S7.** <sup>1</sup>H-NMR spectrum of compound 6 (400 MHz, D<sub>2</sub>O).



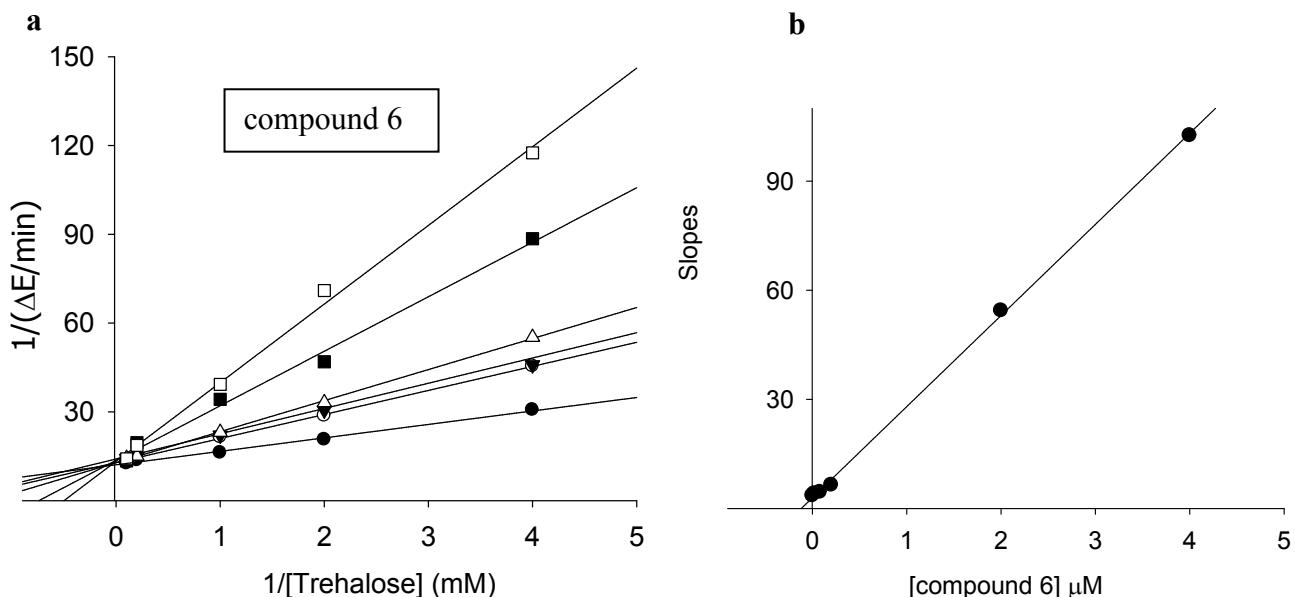
**Figure S8.** <sup>13</sup>C-NMR spectrum of compound 6 (50 MHz, D<sub>2</sub>O).



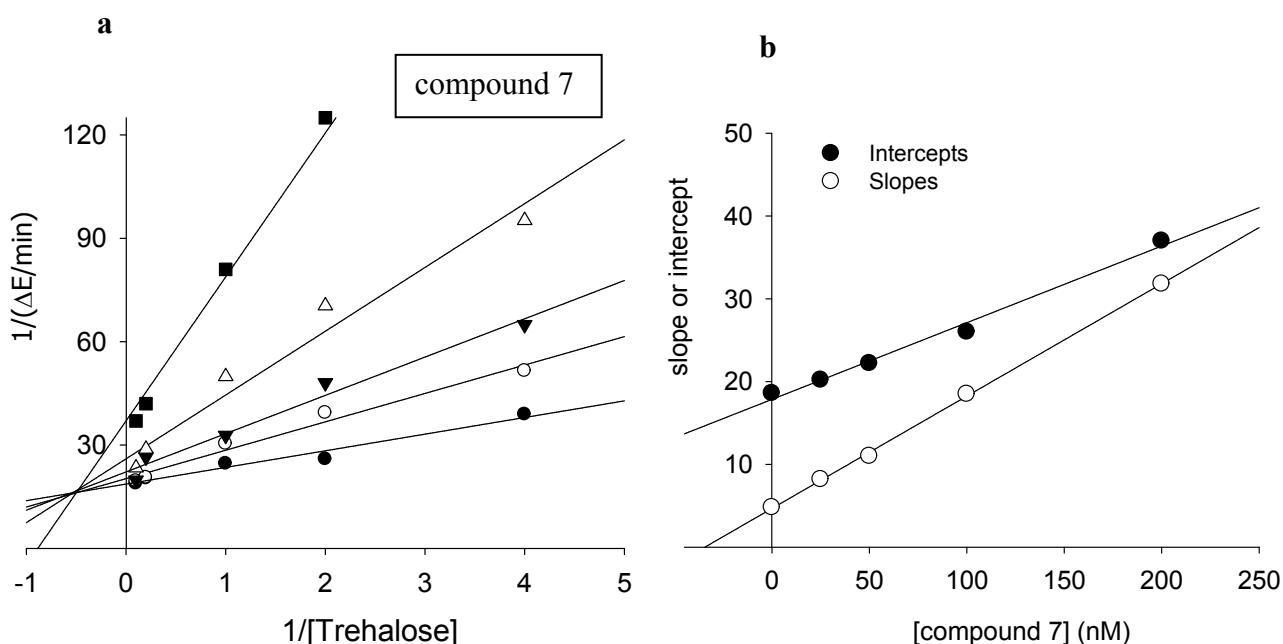
**Figure S9. Inhibition kinetics of midge trehalase in the presence of compound 4.** a) double reciprocal plot in the presence of different fixed inhibitor concentrations (10, 20, 80, 2000 and 4000 nM); b) replot of the slopes and the intercepts of each reciprocal plot versus the corresponding inhibitor concentration; c) secondary replot of  $1/\Delta$  slope and  $1/\Delta$  intercept versus the reciprocal inhibitor concentration.



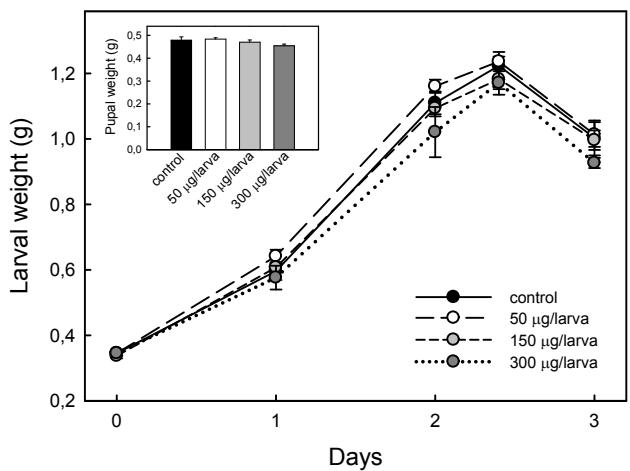
**Figure S10.** Inhibition kinetics of midge trehalase in the presence of compound 5. a) double reciprocal plot in the presence of different fixed inhibitor concentrations ( $0.2, 1, 5 \mu\text{M}$ ); b) replot of the slopes and the intercepts of each reciprocal plot versus the corresponding inhibitor concentration; c) secondary replot of  $1/\Delta$  slope and  $1/\Delta$  intercept versus the reciprocal inhibitor concentration.



**Figure S11.** Inhibition kinetics of midge trehalase in the presence of compound 6. a) double reciprocal plot in the presence of different fixed inhibitor concentrations (20, 80, 200, 2000 and 4000 nM); b) replot of the slopes of each reciprocal plot versus the corresponding inhibitor concentration.



**Figure S12.** Inhibition kinetics of midge trehalase in the presence of compound 7. a) double reciprocal plot in the presence of different fixed inhibitor concentrations (20, 50, 100, and 200 nM); b) replot of the slopes and the intercepts of each reciprocal plot versus the corresponding inhibitor concentration.



**Figure S13.** *S. littoralis* larval and pupal weight after intra-hemocoelical injection of derivative 6. Each experimental group consisted of 16 animals.