

Electronic Supplementary Information for

Design, Synthesis and Biological Evaluation of Light-Driven On-Off Multi-target AChE and MAO-B Inhibitors

Marco Paolino,^{a,*} Mariagrazia Rullo,^{b,†} Samuele Maramai,^{a,†} Modesto de Candia,^b Leonardo Pisani,^b Marco Catto,^b Claudia Mugnaini,^a Antonella Brizzi,^a Andrea Cappelli,^a Massimo Olivucci,^{a,c} Federico Corelli,^a Cosimo D. Altomare.^b

^a Dipartimento di Biotecnologie, Chimica e Farmacia (Dipartimento di Eccellenza 2018-2022), Università degli Studi di Siena, Via A. Moro 2, 53100 Siena, Italy;

^b Department of Pharmacy-Pharmaceutical Sciences, University of Bari Aldo Moro, Via E. Orabona 4, 70125 Bari, Italy.

^c Chemistry Department, Bowling Green State University, USA.

*Corresponding author. E-mail: paolino3@unisi.it

† These authors contributed equally.

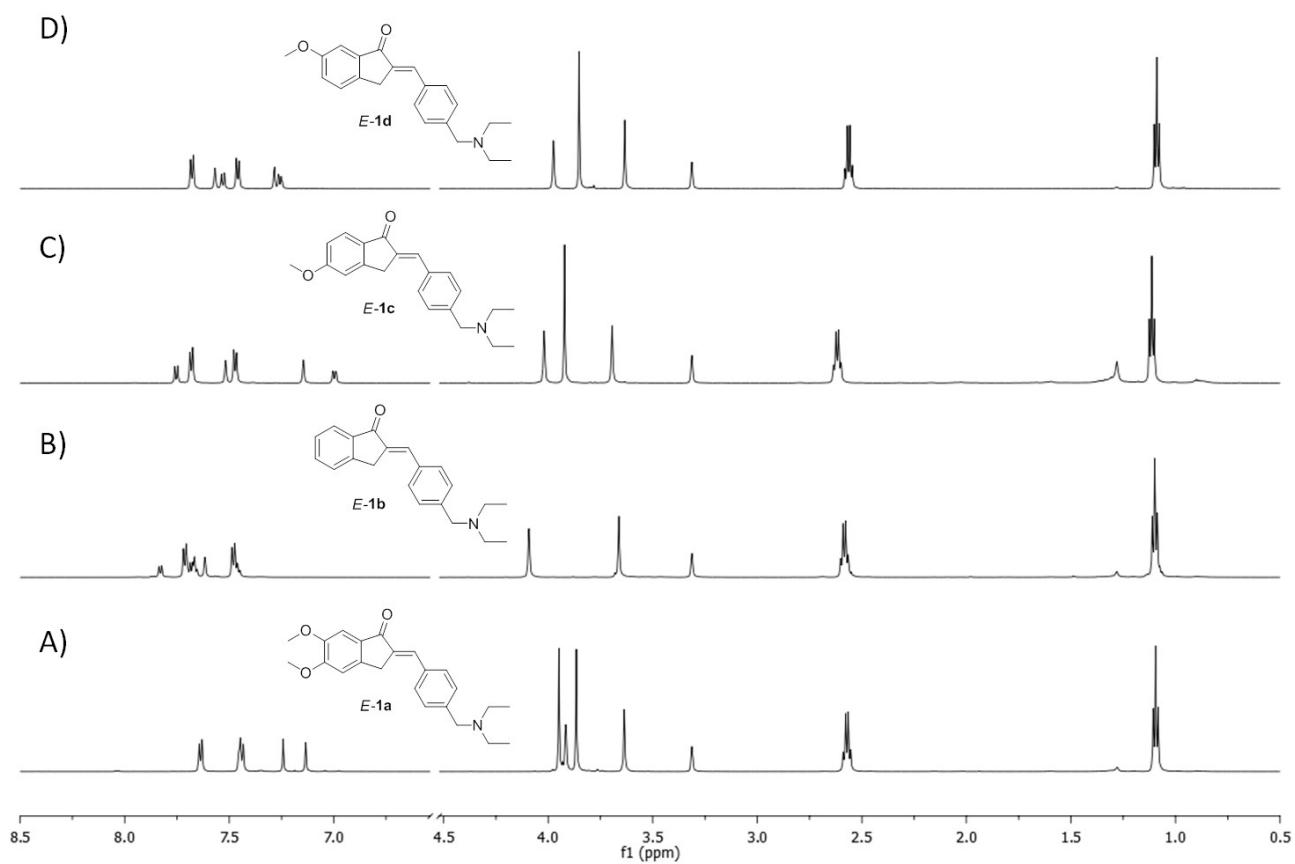


Figure S1. Comparison of the ¹H NMR spectra (CD₃OD, 600 MHz) of compounds A) *E-1a*, B) *E-1b*, C) *E-1c*, and D) *E-1d*.

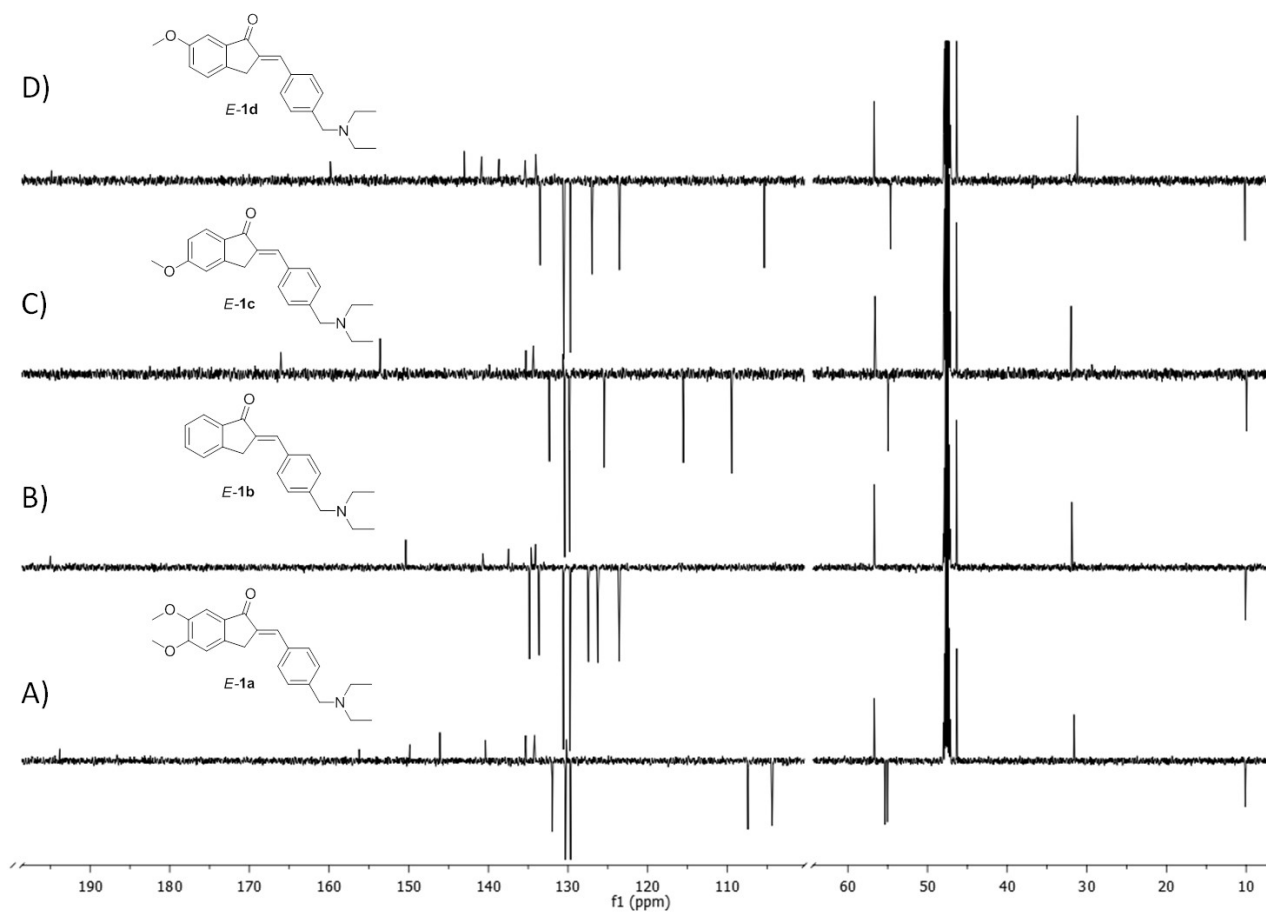


Figure S2. Comparison of the ¹³C DEPT NMR spectra (CD₃OD, 150 MHz) of compounds A) *E-1a*, B) *E-1b*, C) *E-1c*, and D) *E-1d*.

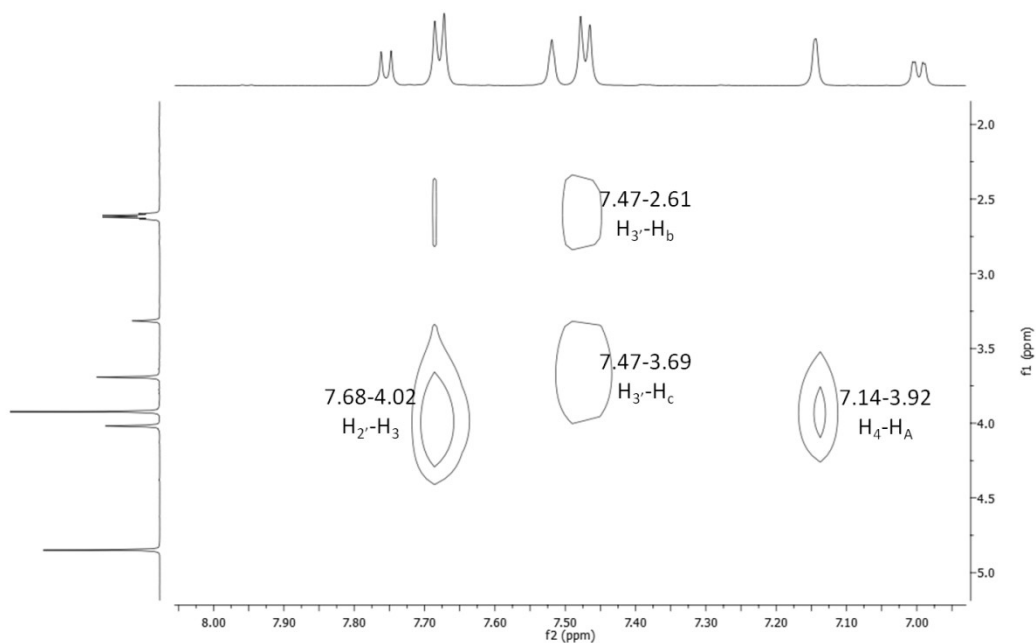


Figure S3. ^1H - ^1H NOESY spectrum of compound *E*-**1c** (CD_3OD , 600 MHz).

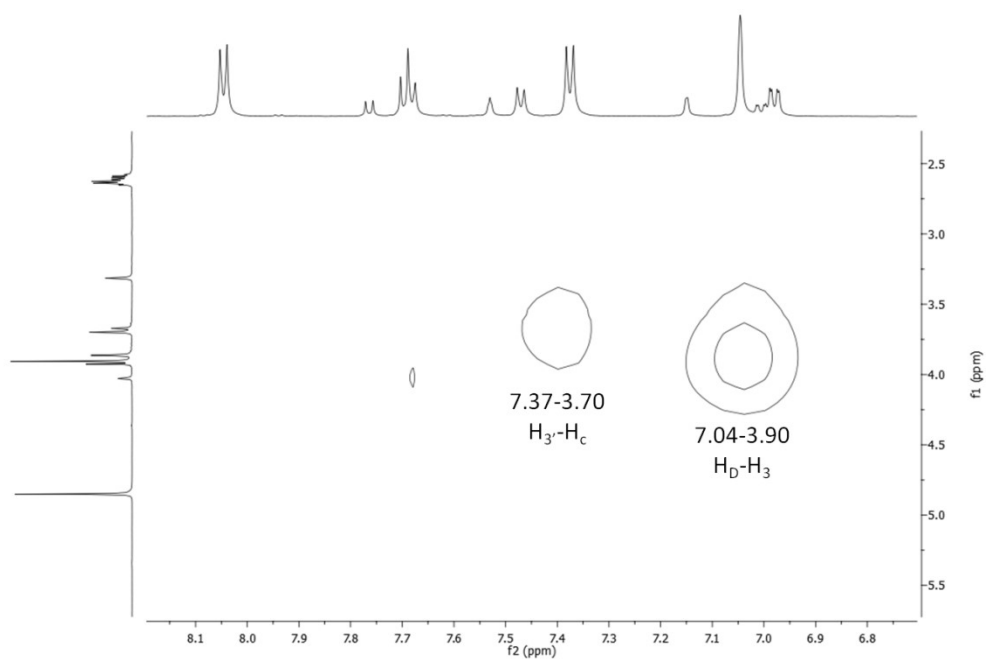


Figure S4. ^1H - ^1H NOESY spectrum (CD_3OD , 600 MHz) of *E/Z* mixture of compound **1c** obtained after UV-B irradiation.

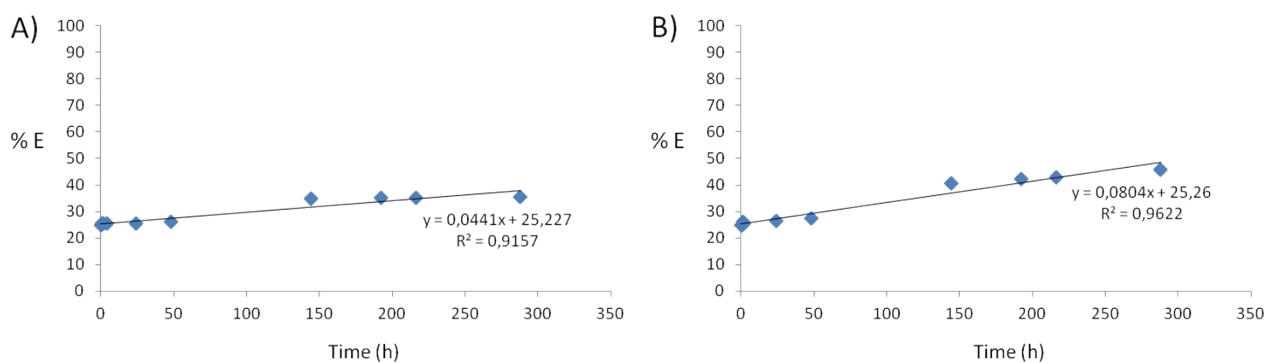


Figure S5. Kinetics of thermal returns of compound Z-1c (from a methanolic solution at PPS obtained by UV-B irradiation) at A) room temperature and B) 50 °C. The *E/Z* ratios have been determined by computing the area of the well distinguishable signals assigned to *E*- and *Z*-isomer in the ^1H NMR spectra.

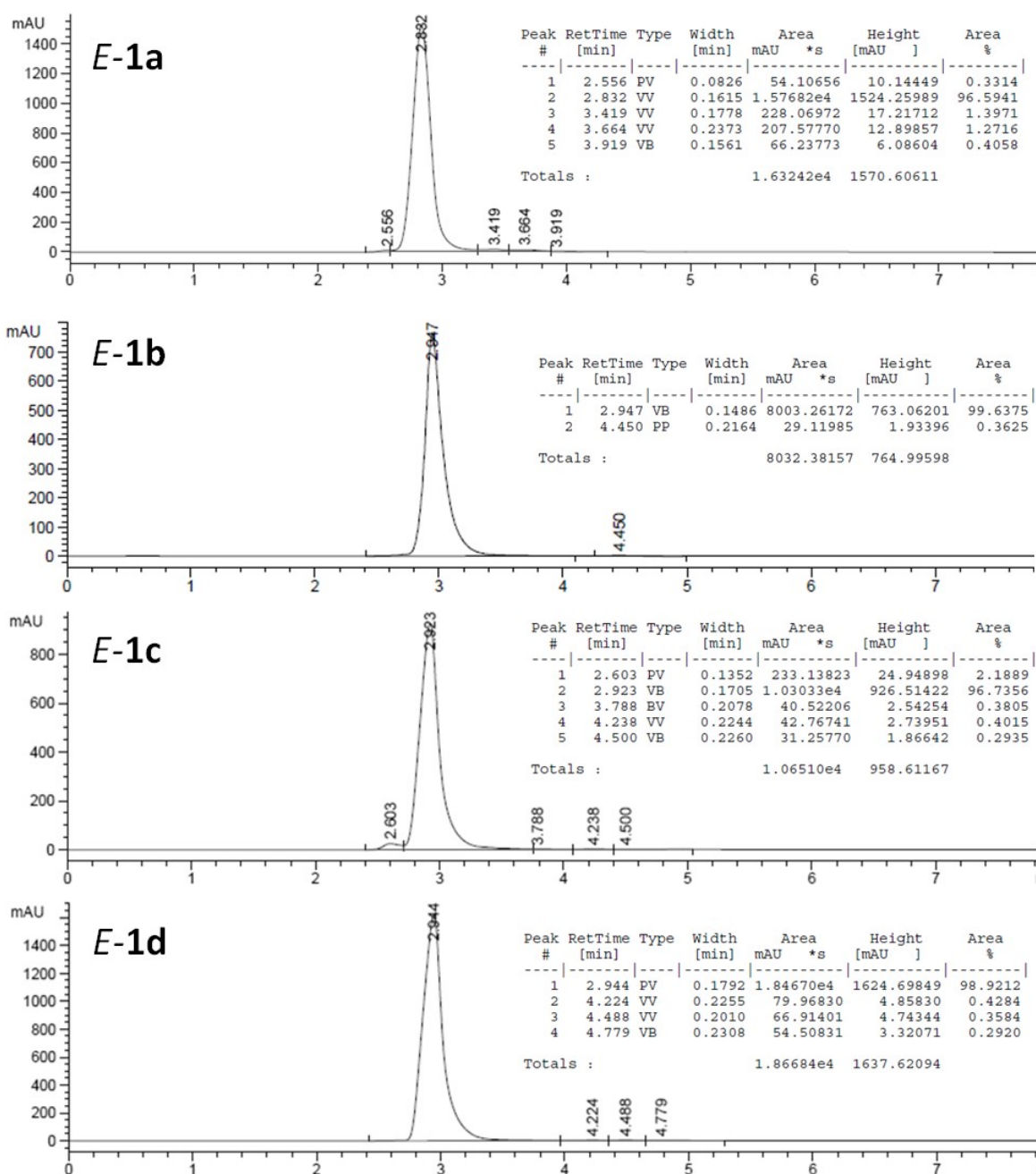


Figure S6. RP-HPLC traces of compounds *E-1a-d*. Purity of compounds was assessed using an Agilent 1100 quaternary pump HPLC apparatus equipped with a Zorbax Eclipse XDB-C8 5 μ (150 $\times$ 4.6 mm). Methanol-H₂O (0.1% formic acid) 80/20 v/v at flow 0.5 mL/min was used as the mobile phase and absorbance at 280 nm has been used for the detection.

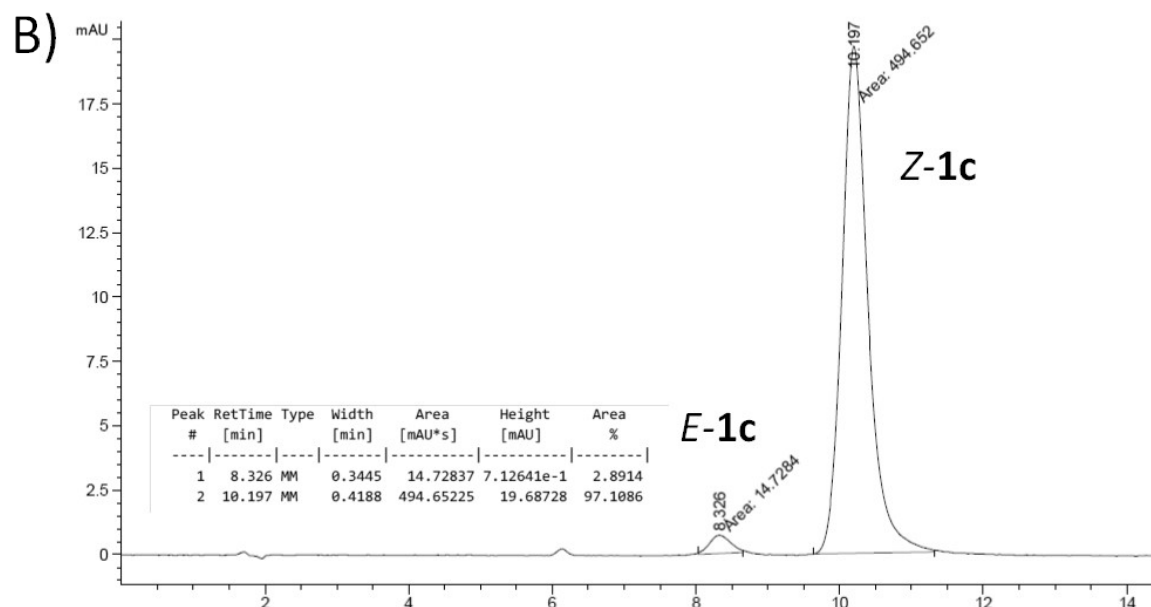
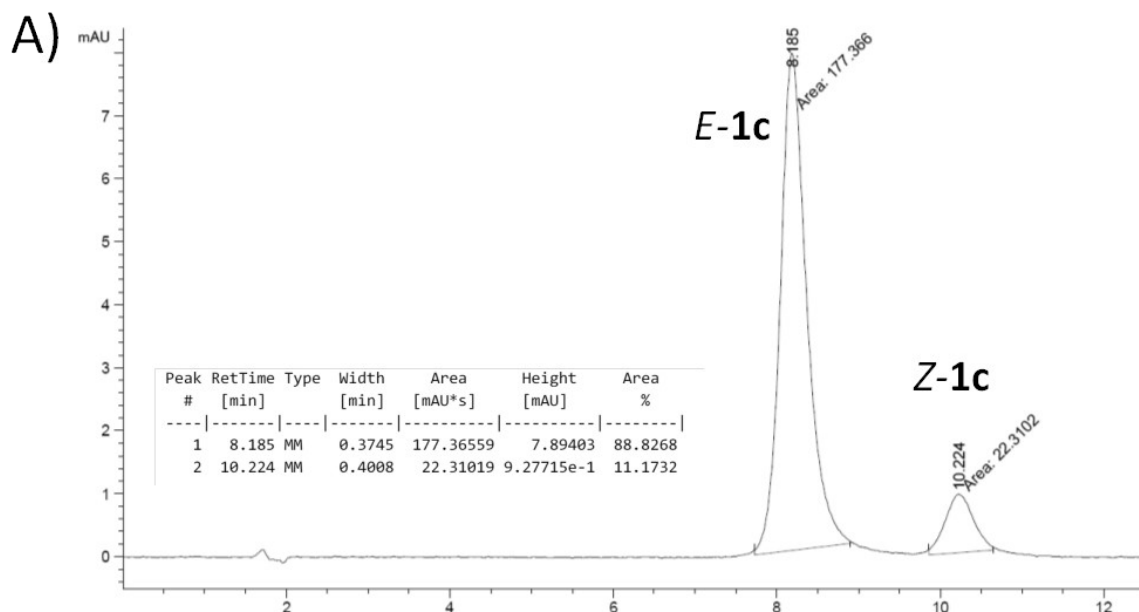


Figure S7. Qualitative analysis of the (A) *E* and (B) *Z* diastereomers of compound **1c** after separation from the *E/Z* mixture. An Agilent 1260 binary pump HPLC apparatus, equipped with a Phenomenex Synergi C18 Fusion-RP 4 μ (150 $\times$ 4.6 mm) has been used. Mobile phase ammonium formate (50 mM, pH 3.5)/methanol 1/1 v/v mixtures, flow 1 mL/min, UV detection with DAD at 330 nm.

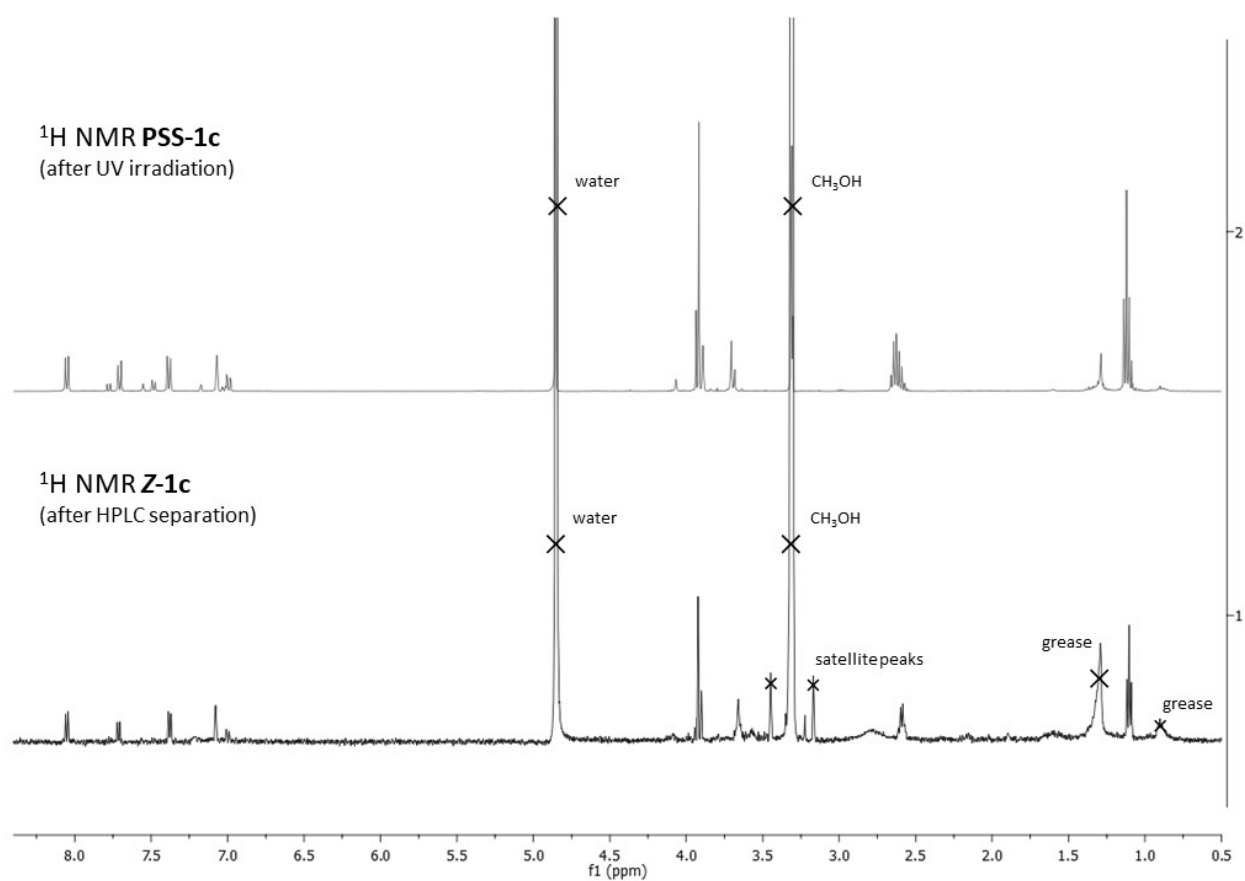


Figure S8. Comparison of the ^1H NMR spectra of **1c** *E/Z* mixture at PSS obtained by UV-B irradiation (up) and **Z-1c** isolated from the *E/Z* mixture by RP-HPLC (down).