

## SUPPLEMENTARY MATERIALS

# Trends in H<sub>2</sub>S-donors Chemistry and Their Effects in Cardiovascular Diseases

Angela Corvino, Francesco Frecentese, Elisa Magli, Elisa Perissutti, Vincenzo Santagada, Antonia Scognamiglio, Giuseppe Caliendo, Ferdinando Fiorino, Beatrice Severino\*

Department of Pharmacy, School of Medicine, University of Naples «Federico II», Via D. Montesano, 49, 80131, Napoli, Italy; [angela.corvino@unina.it](mailto:angela.corvino@unina.it) (A.C.); [frecente@unina.it](mailto:frecente@unina.it) (F.Fr.); [elisa.magli@unina.it](mailto:elisa.magli@unina.it) (E.M.); [perissut@unina.it](mailto:perissut@unina.it) (E.P.); [santagad@unina.it](mailto:santagad@unina.it) (V.S.); [antonia.scognamiglio@unina.it](mailto:antonia.scognamiglio@unina.it) (A.S.); [caliendo@unina.it](mailto:caliendo@unina.it) (G.C.); [fefiorin@unina.it](mailto:fefiorin@unina.it) (F.Fi.)

\*Correspondence: [bseverin@unina.it](mailto:bseverin@unina.it) (B.S.); Tel. +39081679828

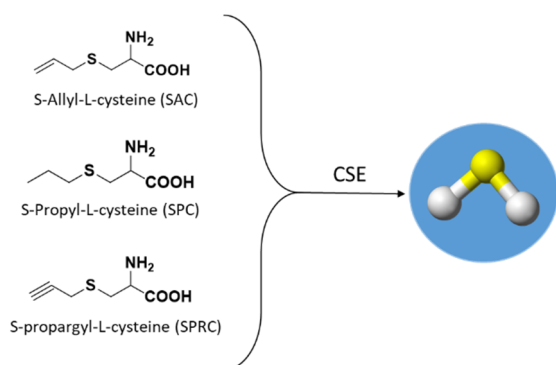


Figure S1. The chemical structures of SAC, SPC and SPRC.

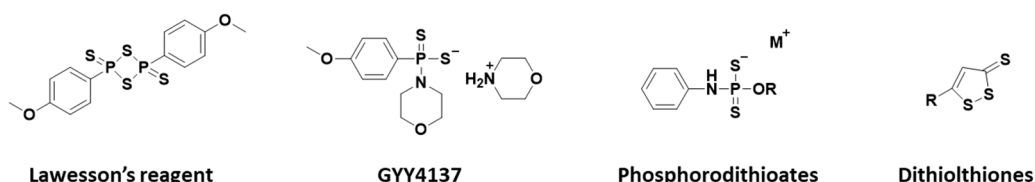


Figure S2. Chemical structures of hydrolysis-triggered H<sub>2</sub>S donors.

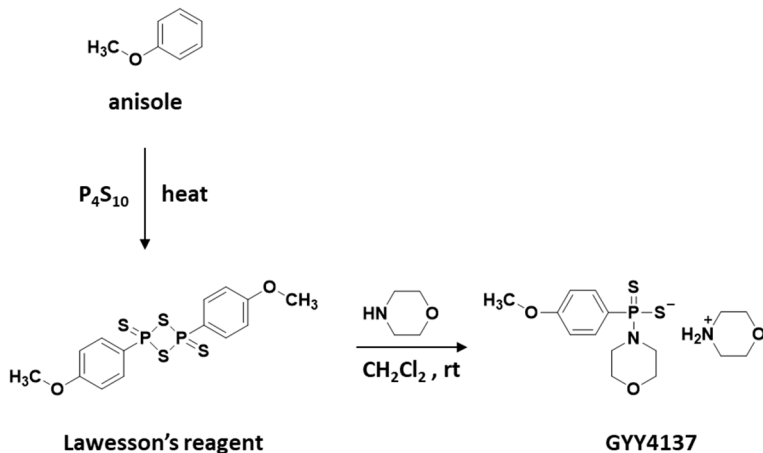
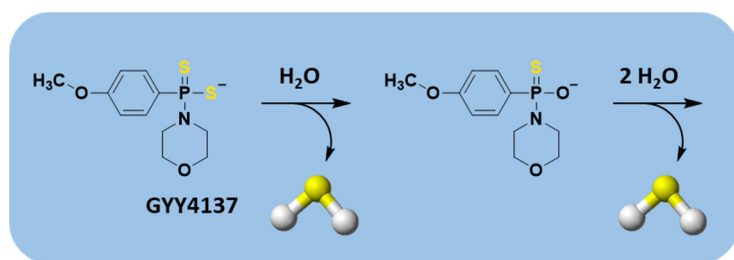
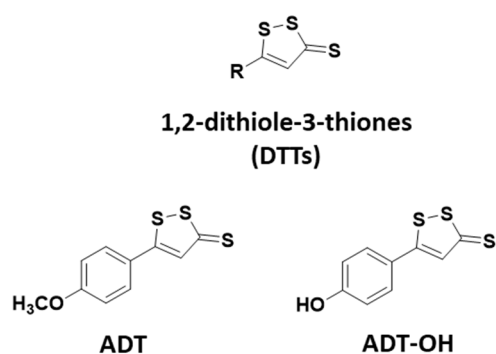


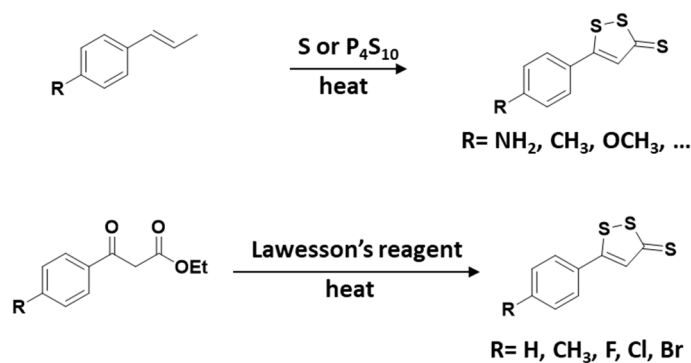
Figure S3. Chemical synthesis of GYY4137.



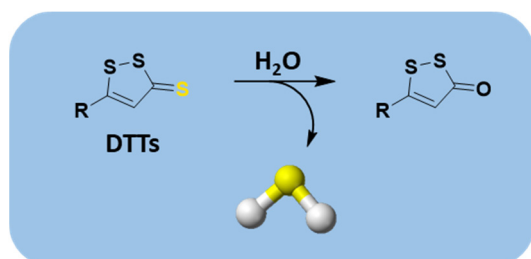
**Figure S4.** The hydrolytic degradation of GYY4137 and the H<sub>2</sub>S release.



**Figure S5.** Structures of the most used DTTs as H<sub>2</sub>S donors.



**Figure S6.** Different chemical strategies to synthesize DTTs.



**Figure S7.** Mechanism of H<sub>2</sub>S release from DTTs.

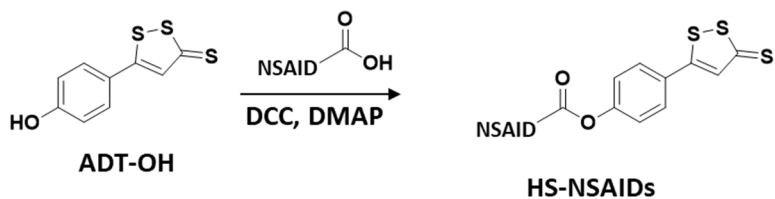


Figure S8. Chemical synthesis of HS-NSAIDs.

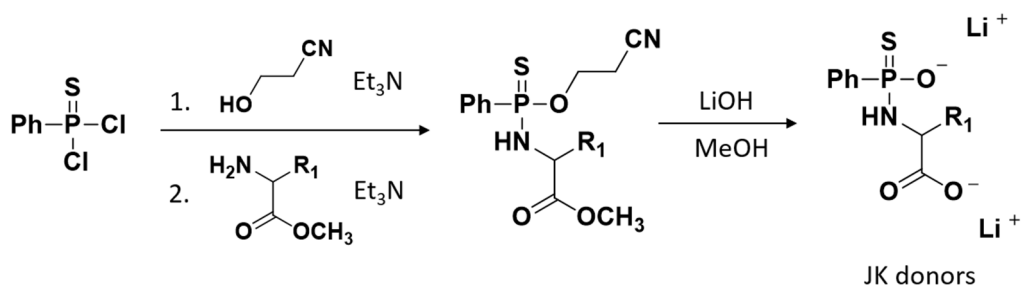


Figure S9. Synthetic strategy to obtain JK donors.

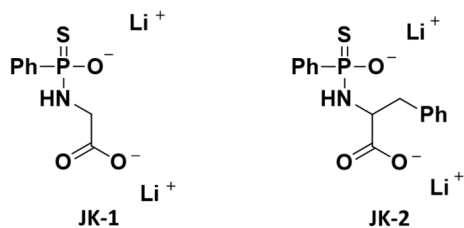


Figure S10. Chemical structures of two main JK donors.

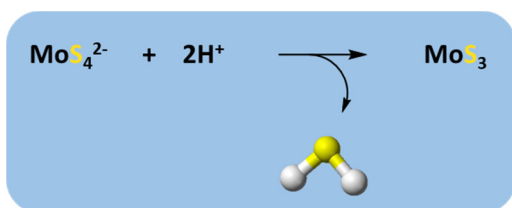
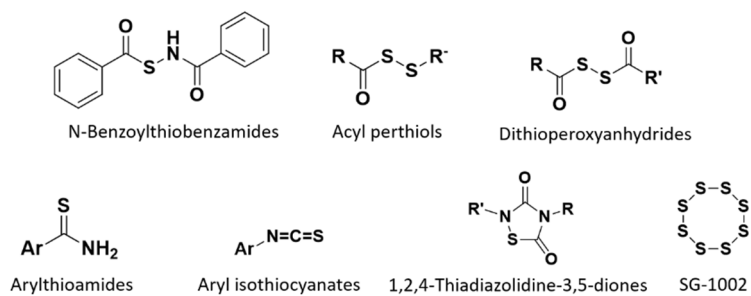
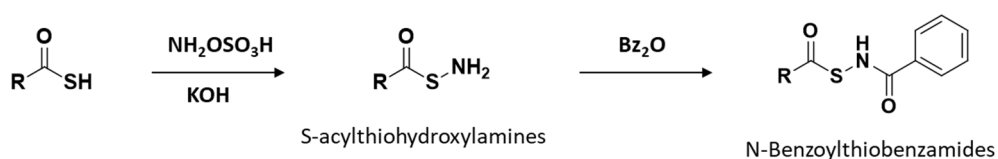


Figure S11. The H<sub>2</sub>S release from ammonium tetrathiomolybdate (ATTM).



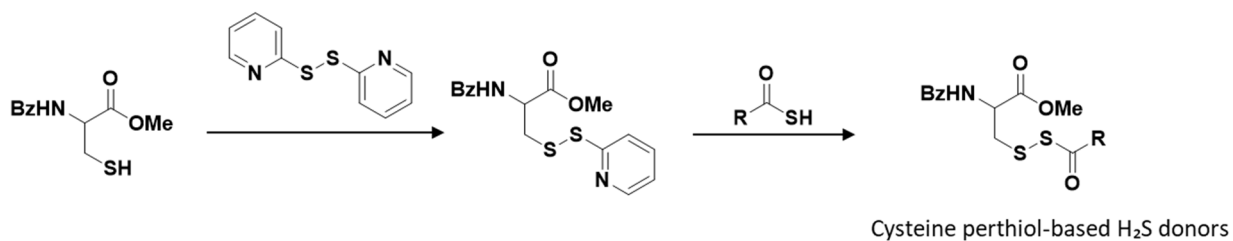
**Figure S12.** Chemical structures of thiol triggered H<sub>2</sub>S donors with cardioprotective activity.



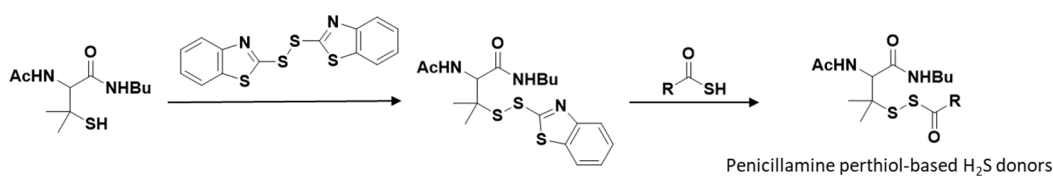
**Figure S13.** Chemical synthesis of N-(benzoylthio)benzamides.



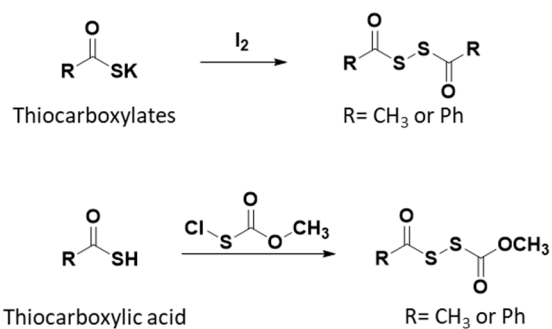
**Figure S14.** Chemical structures of perthiol-based donors.



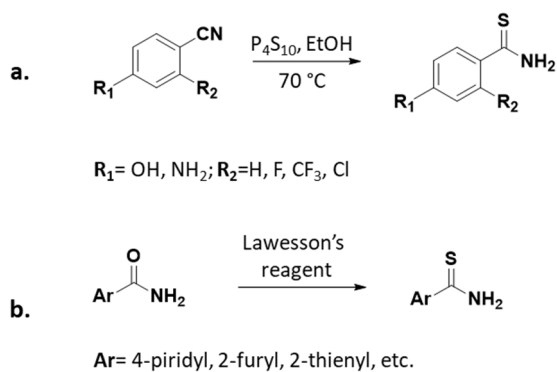
**Figure S15.** Synthetic route to obtain cysteine perthiol-based donors.



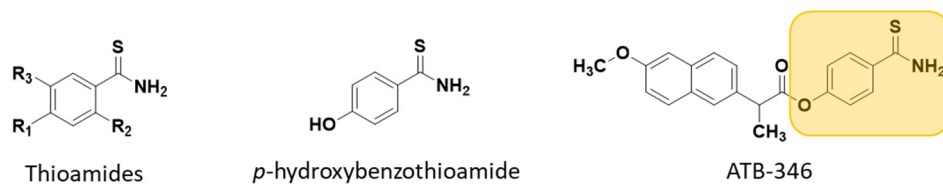
**Figure S16.** Chemical synthesis of penicillamine perthiol-based donors.



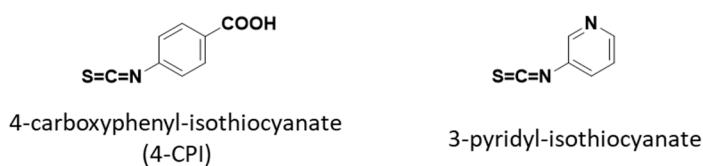
**Figure S17.** The synthetic strategies to obtain dithioperoxyanhydride-based H<sub>2</sub>S.



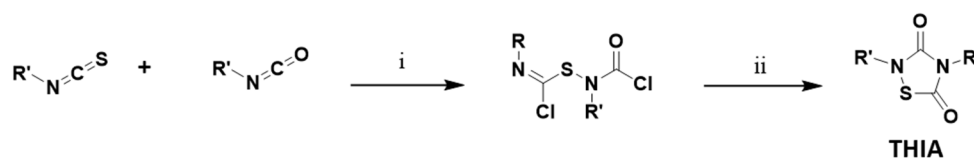
**Figure S18.** Chemical synthesis of a) non-heterocyclic and b) heterocyclic *p*-hydroxy-arylthio-amides.



**Figure S19.** The thioamides: general structure, chemical structures of lead compound (*p*-hydroxybenzothioamide) and its hybrid with naproxen (ATB-346).



**Figure S20.** Chemical structures of two aryl isothiocyanates exhibiting cardioprotective activity.



**Figure S21.** Synthesis of THIA. Conventional synthetic strategy: (i) SO<sub>2</sub>Cl<sub>2</sub>/diethyl ether, 24h; (ii) H<sub>2</sub>O, reflux, 30 min; microwave-assisted synthesis: (i) SO<sub>2</sub>Cl<sub>2</sub>/diethyl ether/MW 500W, 50 °C, 1h; (ii) H<sub>2</sub>O, MW 500W, 120 °C, 30 min.

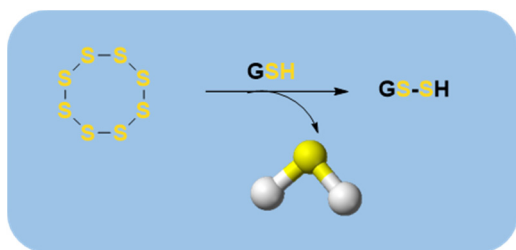
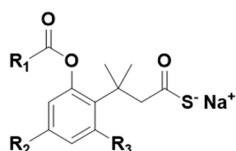


Figure S22. Mechanism of H<sub>2</sub>S release from SG1002.



HP-101, R<sub>1</sub>=CH<sub>3</sub>; R<sub>2</sub>=CH<sub>3</sub>; R<sub>3</sub>=CH<sub>3</sub>

HP-102, R<sub>1</sub>= ; R<sub>2</sub>=CH<sub>3</sub>; R<sub>3</sub>=CH<sub>3</sub>

Figure S23. Chemical structures of "TML"-based H<sub>2</sub>S prodrugs HP-101 and HP-102.

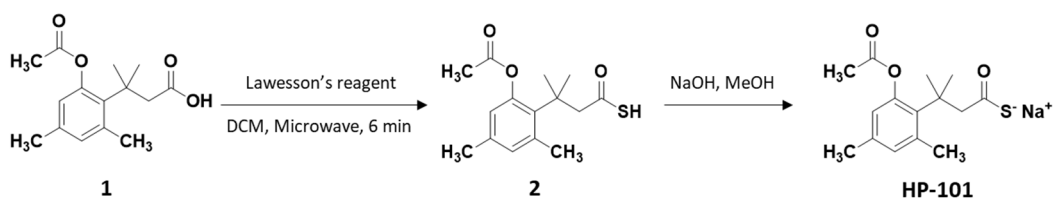


Figure S24. Synthesis of "TML"-based H<sub>2</sub>S prodrug HP-101.



N-thiocarboxyanhydrides  
(NTAs)

NTA1

Figure S25. Chemical structures of N-thiocarboxyanhydrides (NTAs) and sarcosine NTA derivative (NTA1).

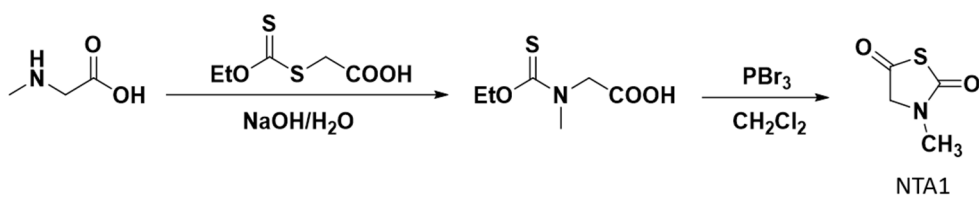
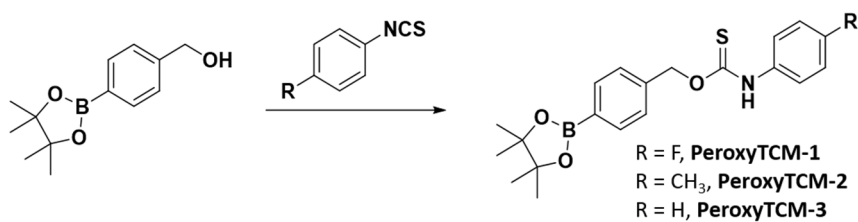
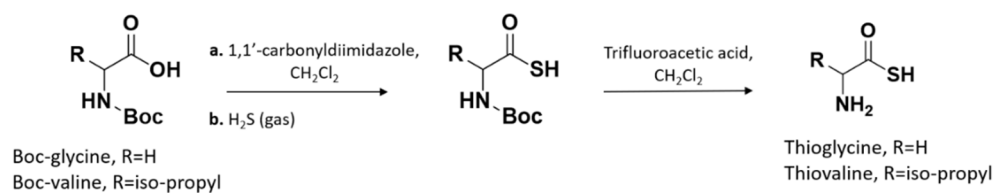


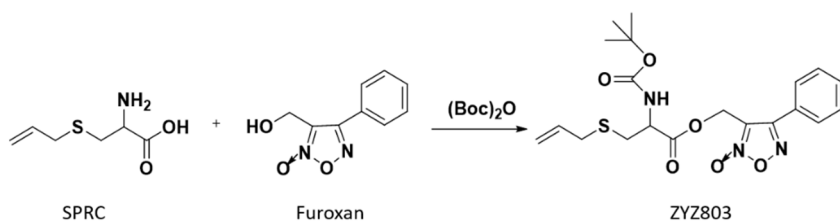
Figure S26. Chemical synthesis of sarcosine NTA derivative (NTA1).



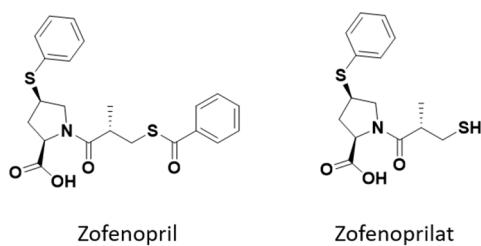
**Figure S27.** Chemical structures and synthesis of ROS-activated H<sub>2</sub>S donors.



**Figure S28.** Synthesis of thioamino acids.



**Figure S29.** Chemical structure and synthesis of ZYZ803.



**Figure S30.** Chemical structures of a) zofenopril and b) its active metabolite, zofenoprilat.