Metabolism, pharmacokinetics, tissue distribution, and stability studies of the prodrug analog of an anti-HBV dinucleoside phosphorothioate

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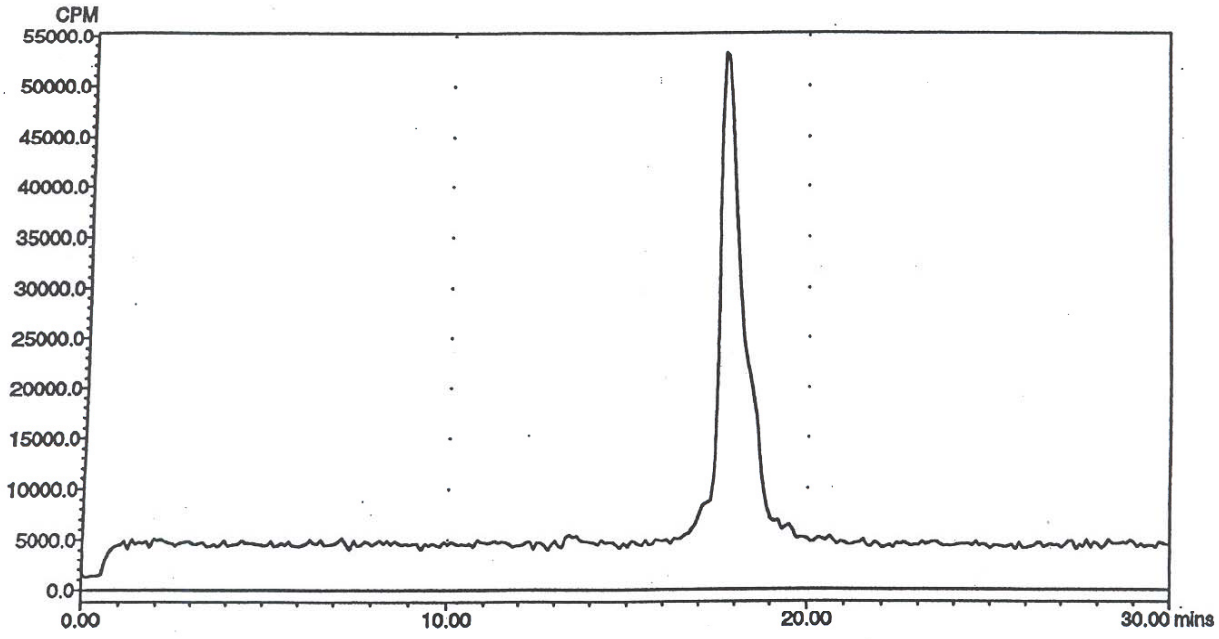
KGO, CEG, JCM: Toxicology & Pharmacokinetics, SRI International, Menlo Park, CA 94025
JM: Genzyme Corporation, Marlborough, Massachusetts



Regions: ^{14}C Detector: FSA

Name	Start (mins)	End (mins)	Retention (mins)	Height (CPM)	Area (CPM)	%ROI (%)	%Total (%)
No ROIs allocated.							
0 Peaks					0.0	100.00	0.00

Supplemental Fig. 1. Radiochromatogram of **^{35}S-**2 used in the studies. Radio HPLC was carried out using a Waters Nova Pak C18 column (4 µM, 4.6 X 250 mm), using an elution gradient of A to B consisting of 0.1 M ammonium acetate (A) and 0.1 M ammonium acetate:acetonitrile (20:80) (B) over 30 min at a flow rate of 1.5 ml/min. Detection of UV-absorbing compounds were done by UV detector at 254 nm and that of radioactive compounds by Radiomatic 610 TR detector.

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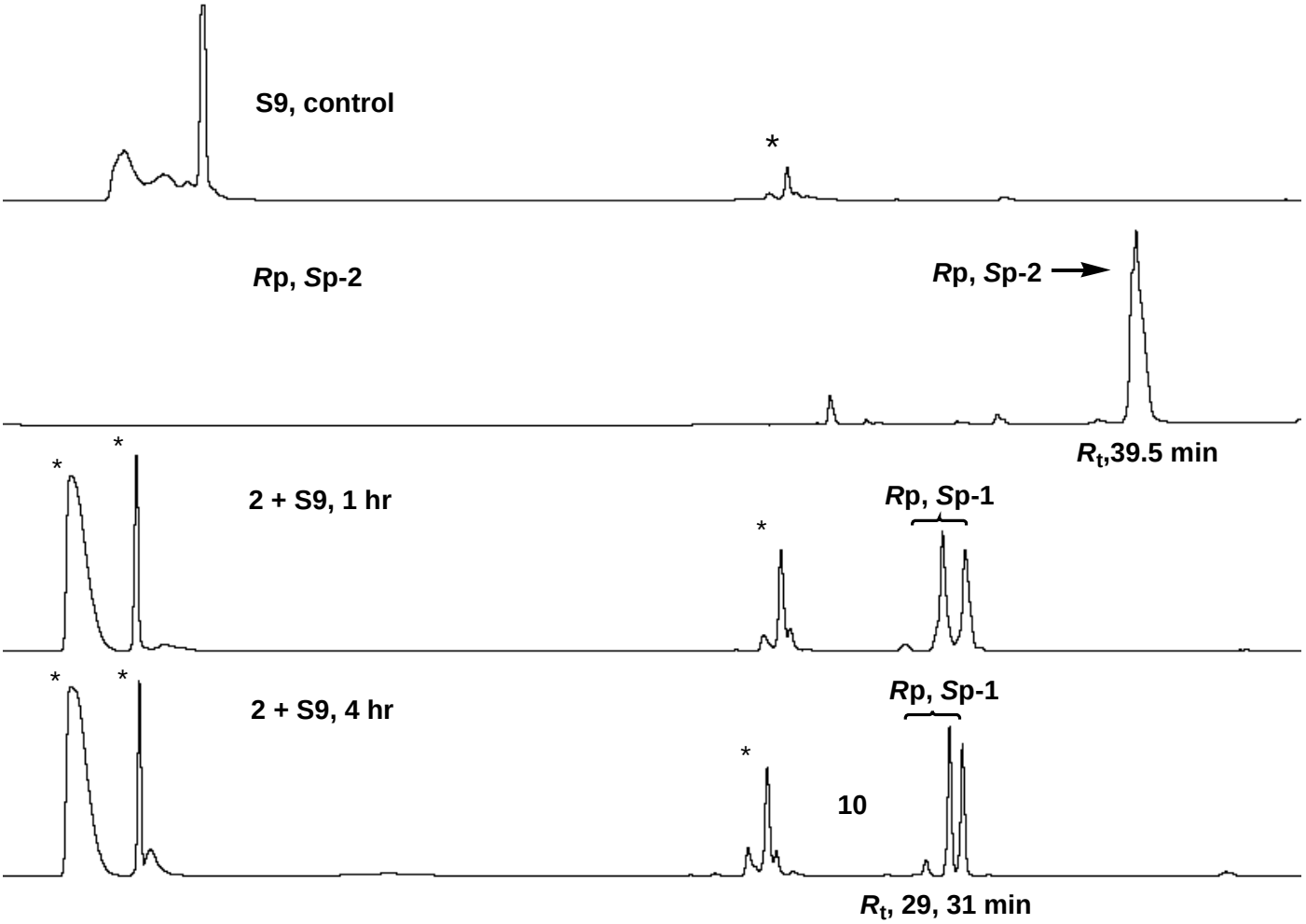

Supplemental Fig. 2. Representative HPLC profile at different time points of aliquots from the incubation of ***R*p,- *S*p-2** with human liver S9 fractions. The peaks with asterisks correspond to the components from S9 fraction.

Drug Metabolism and Disposition

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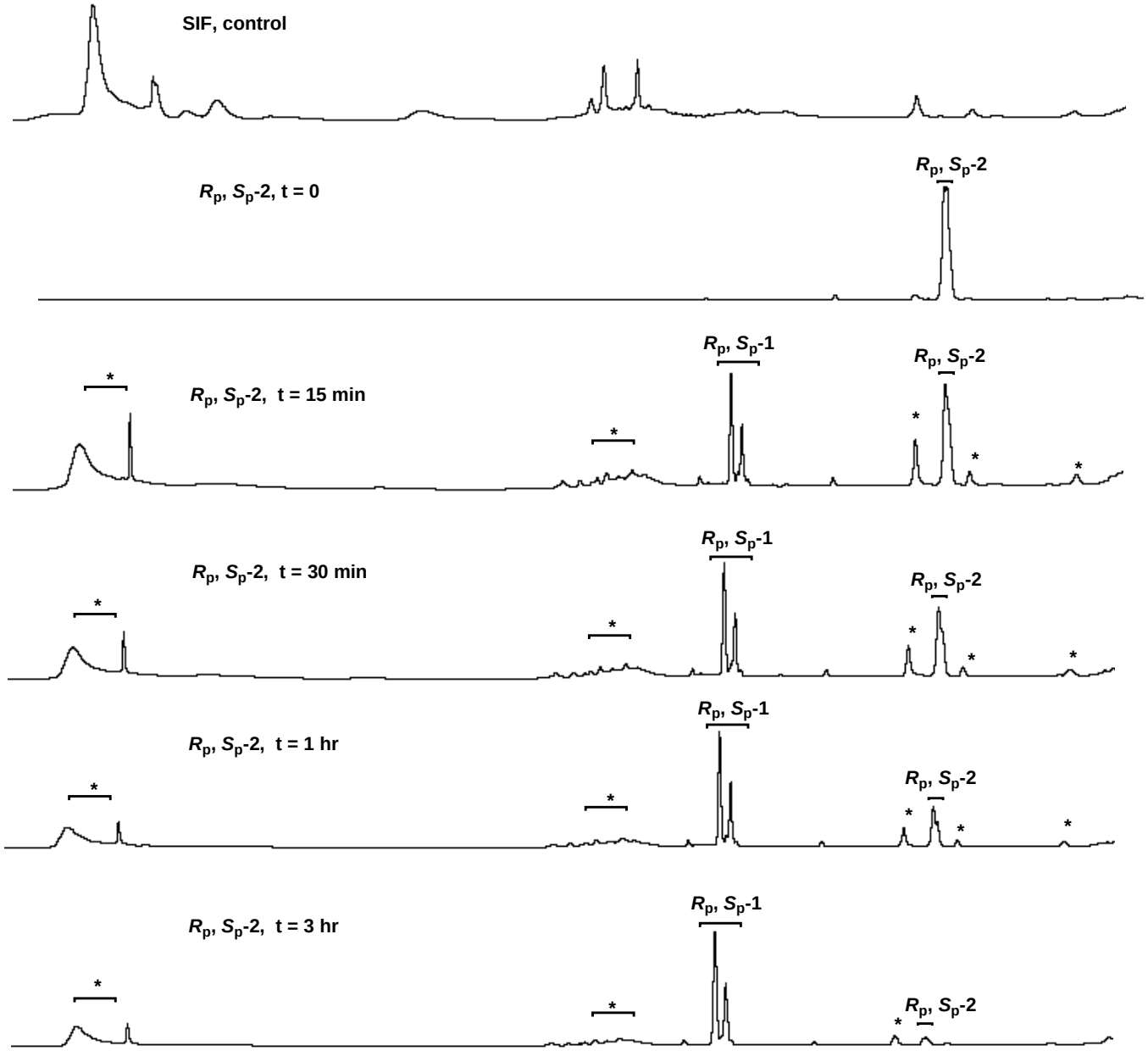

Supplemental Fig. 3. Time-course HPLC profiles of incubates of ***R*p-, *S*p-2** showing the formation of ***R*p-, *S*p-1** in simulated intestinal fluid. The peaks with asterisks correspond to the components from SIF.

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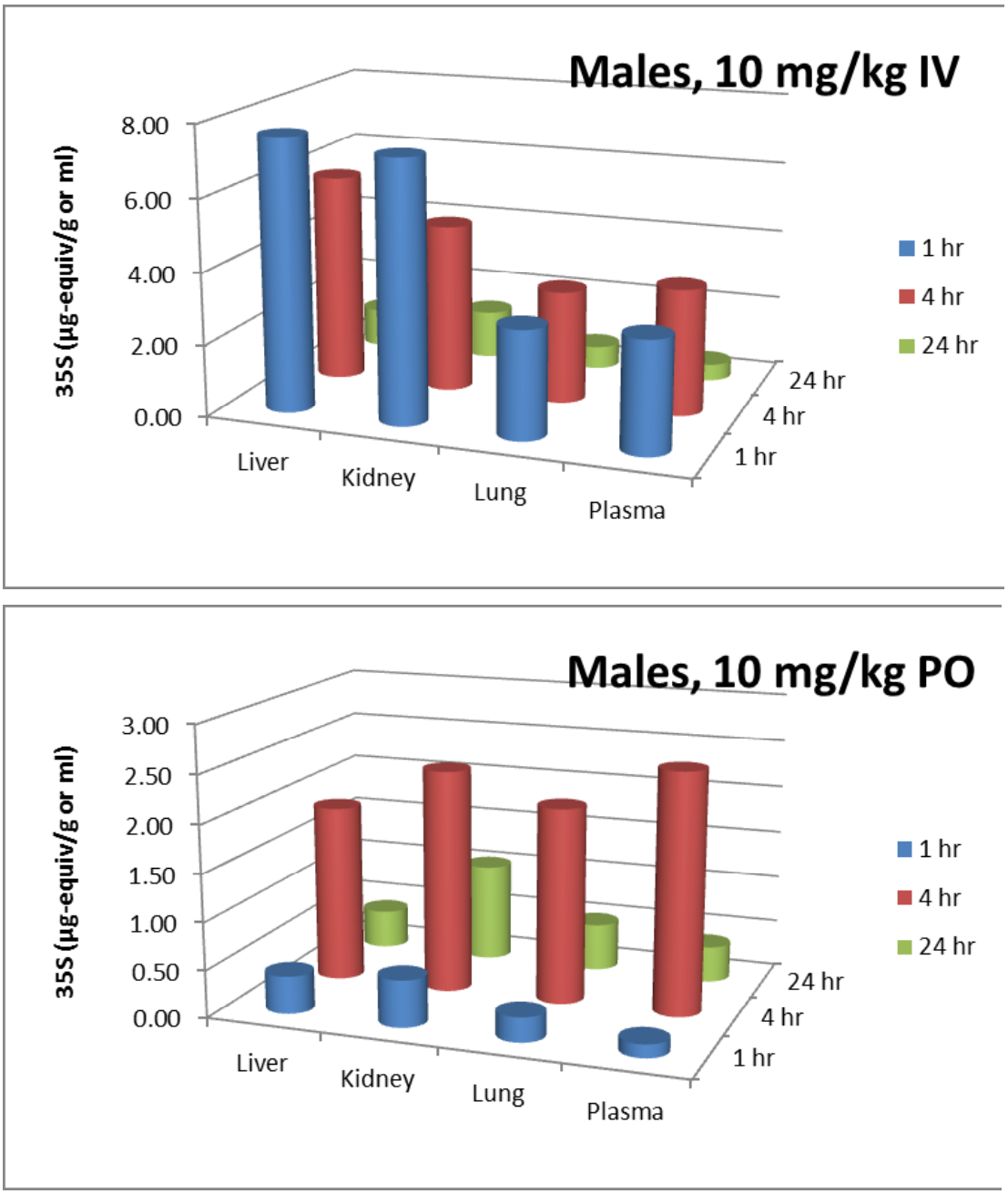

Supplemental Fig. 4. Concentration of radioactivity after a single i.v. or p.o. dose of **^{35}S-2** in major tissues (µg-equiv/ml plasma or g tissue) from male rats at 1, 4 and 24 h after dose administration. Data is presented as mean values derived at each time point from nine rats.

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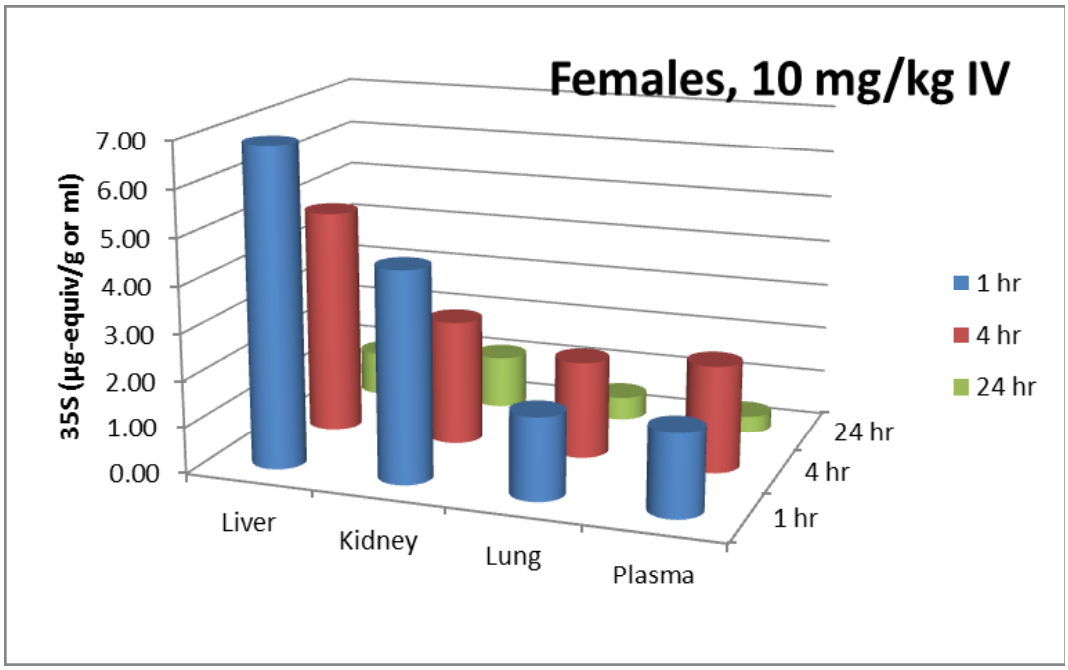

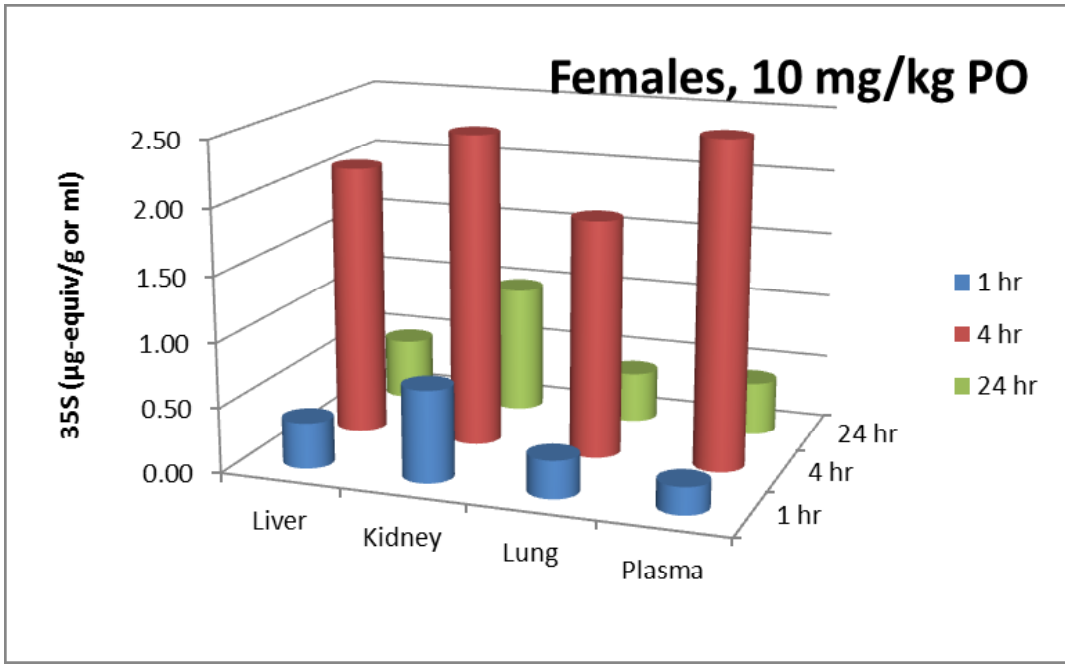

Supplemental Fig. 5. Concentration of radioactivity after a single i.v. or p.o. dose of **^{35}S-2** in major tissues (µg-equiv/ml plasma or g tissue) from female rats at 1, 4 and 24 h after dose administration. Data is presented as mean values derived at each time point from nine rats.