Electronic Supplementary Material (ESI) for Analyst.


# Supporting Information for

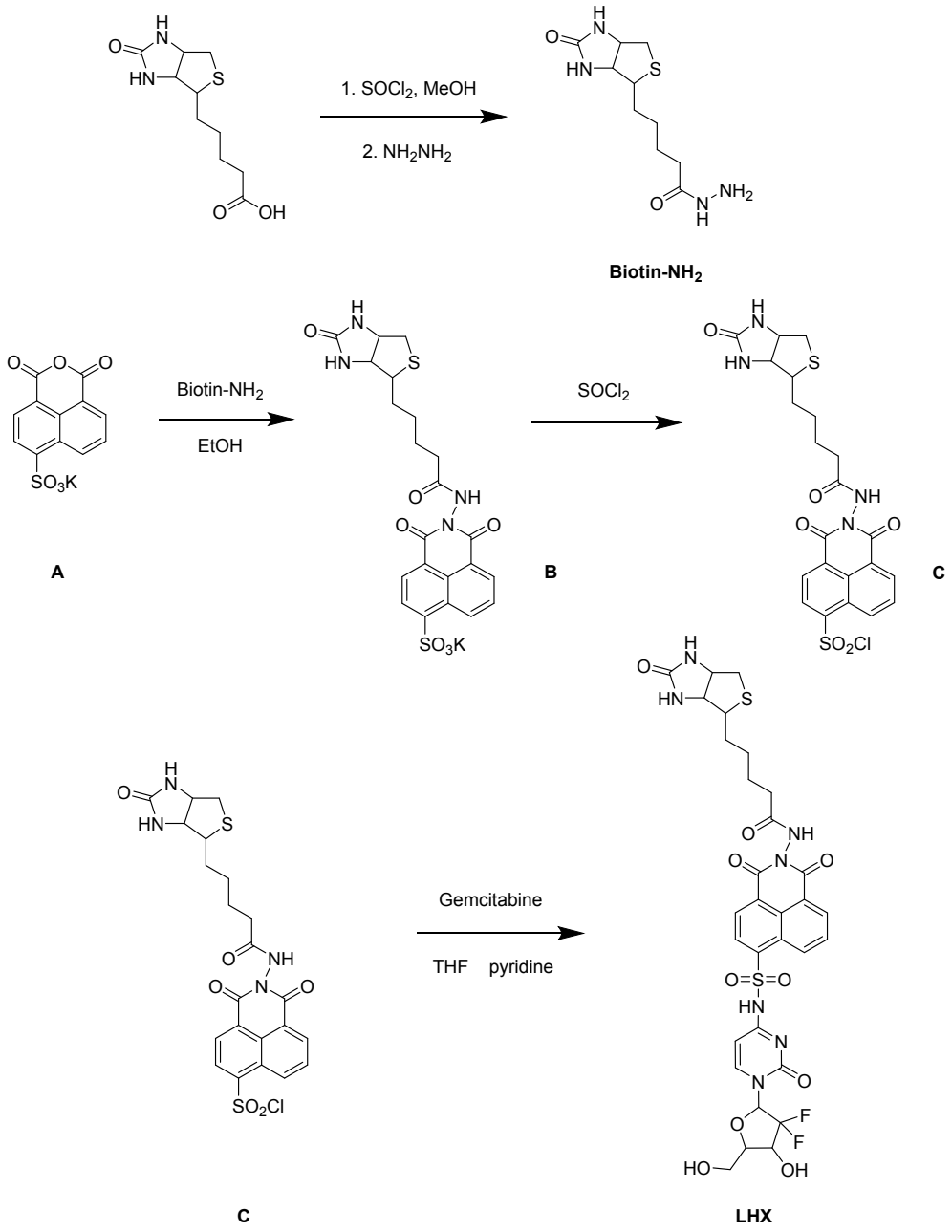
## Evaluation of GSH-generating prodrug via sulfonamide-induced "integrative" platform for selective cancer therapy

Jun Liu*, Cheng Cao

*College of Chemistry and Chemical Engineering, Hexi University, Zhangye City 734000, Gansu Province, P. R. China*

*Corresponding Author; Email: liujun3622849@163.com

# Table of contents




**Scheme S1.** Synthesis of LHX

**Synthesis of B**

To a solution of 4-sulfo-1,8-naphthalic anhydride potassium salt (2 g, 6 mmol) in ethanol (100 ml) under an argon atmosphere was added Biotin-$NH_2$ (3.1 g, 12 mmol). After the reaction mixture was refluxed for 2.5 h, the residue was cooled to room temperature, filtered and washed with ethanol. The obtained cream residue B in 63% yield was without further purified according to the previous literatures. $^1$H NMR (500 MHz, DMSO) δ 10.21 (s, 2H), 8.93 (s, 1H), 8.58 (d, $J$ = 0.9 Hz, 1H), 8.56 (d, $J$ = 7.6 Hz, 1H), 8.34 (s, 1H), 8.24 (s, 1H), 8.01 (s, 1H), 4.33 (m, 1H), 4.13 (s, 2H), 3.58 (s, 1H), 2.73 (s, 1H), 2.00 (d, $J$ = 7.5 Hz, 2H), 1.61 (d, $J$ = 2.5 Hz, 2H), 1.50 (d, $J$ = 7.3 Hz, 2H), 1.26 (d, $J$ = 9.7 Hz, 2H). ESI-MS: m/z calcd for $[C_{22}H_{21}KN_4O_7S_2]^+$, 556.05; found, 557.3 $(M)^+$.

**Synthesis of C, LHX**

To a solution of B (473 mg, 0.85 mmol) under an argon atmosphere was added $SOCl_2$ (20 ml) and a catalytic amount of DMF. After the result solution was refluxed for 12 h, the solvent removal under reduced pressure. The residue C was used directly to the next reaction. To a solution of benzylamine (224 mg, 0.85mmol) in anhydrous THF (20 ml) under argon atmosphere was added the pyridine (2 ml). After the reaction mixture was stirred for 10 min, a solution of C (456 mg, 0.85 mmol) in THF (20 ml) was added dropwise at 0℃. After the result solution was refluxed for 12 h, the solvent removal under reduced pressure. The residue was purified by silica column hexane: dichloromethane=1:9 to obtain LHX (374 mg, 0.49 mmol) as pale-yellow solid in 61% yield. 1H NMR (500 MHz, DMSO) δ 12.02 (s, 1H), 9.32 (d, J = 8.6 Hz, 1H), 8.51 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 7.5 Hz, 1H), 7.94 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.44 (s, 1H), 6.46 (s, 1H), 6.40 (s, 1H), 6.26 (s, 1H), 6.14 (s, 1H), 5.82 (d, J = 7.5 Hz, 1H), 5.22 (s, 1H), 4.32 (s, 2H), 4.15 (s, 2H), 3.78 (d, J = 16.0 Hz, 2H), 3.63 (d, J = 12.1 Hz, 1H), 3.40 (s, 2H), 3.11 (d, J = 7.4 Hz, 1H), 2.81 (s, 1H), 2.59 (d, J = 12.4 Hz, 1H), 2.21 (t, J = 7.4 Hz, 2H), 1.51 (d, J = 8.1 Hz, 2H), 1.34 (d, J = 15.3 Hz, 2H). ESI-MS: m/z calcd for $[C_{31}H_{31}F_2N_7O_{10}S_2]^+$, 763.15; found, 764.3 $(M)^+$.

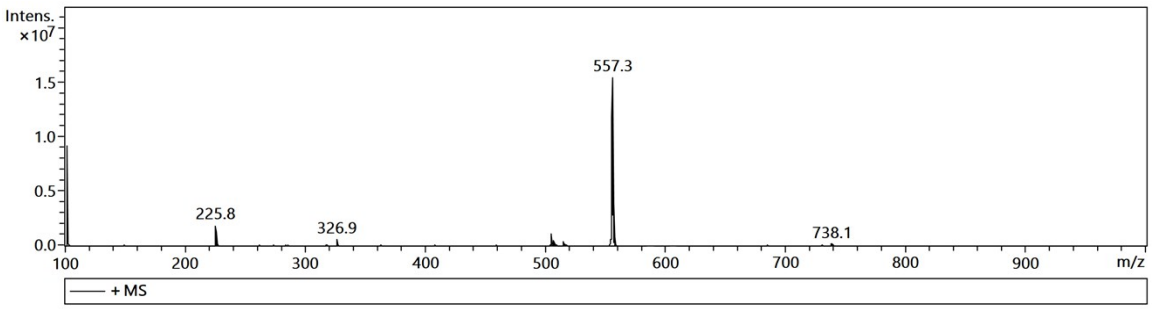



**Figure S1.** Mass spectrum of compound B.

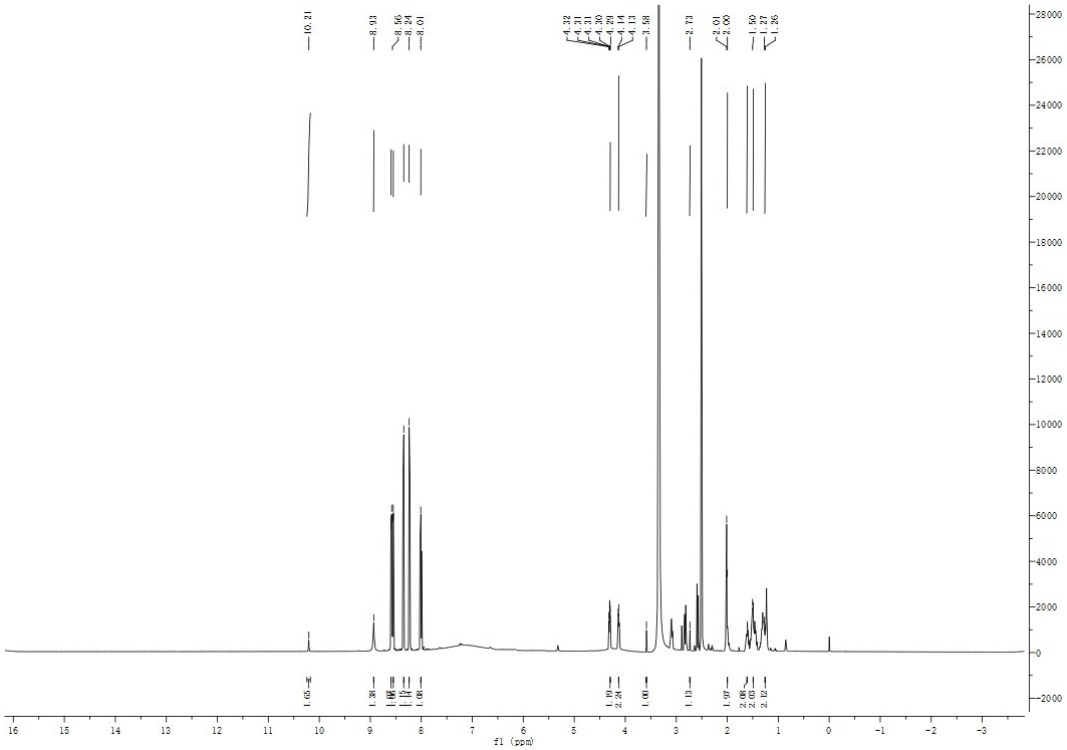



**Figure S2.** $^{1}$H NMR of compound B.

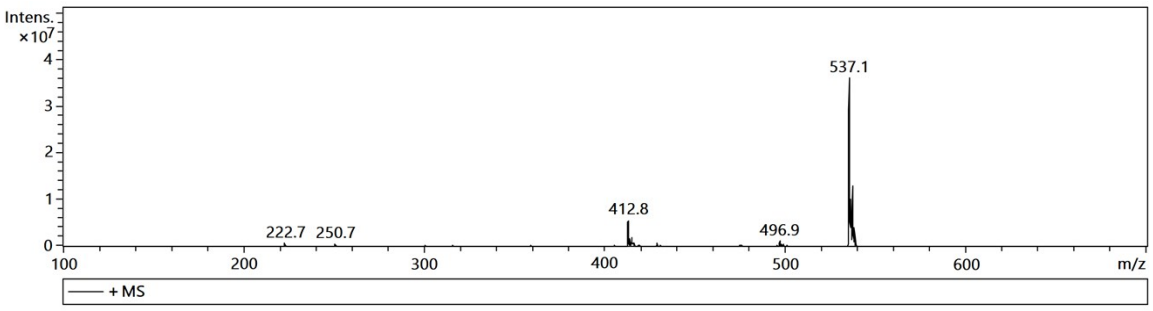



**Figure S3.** Mass spectrum of compound C.

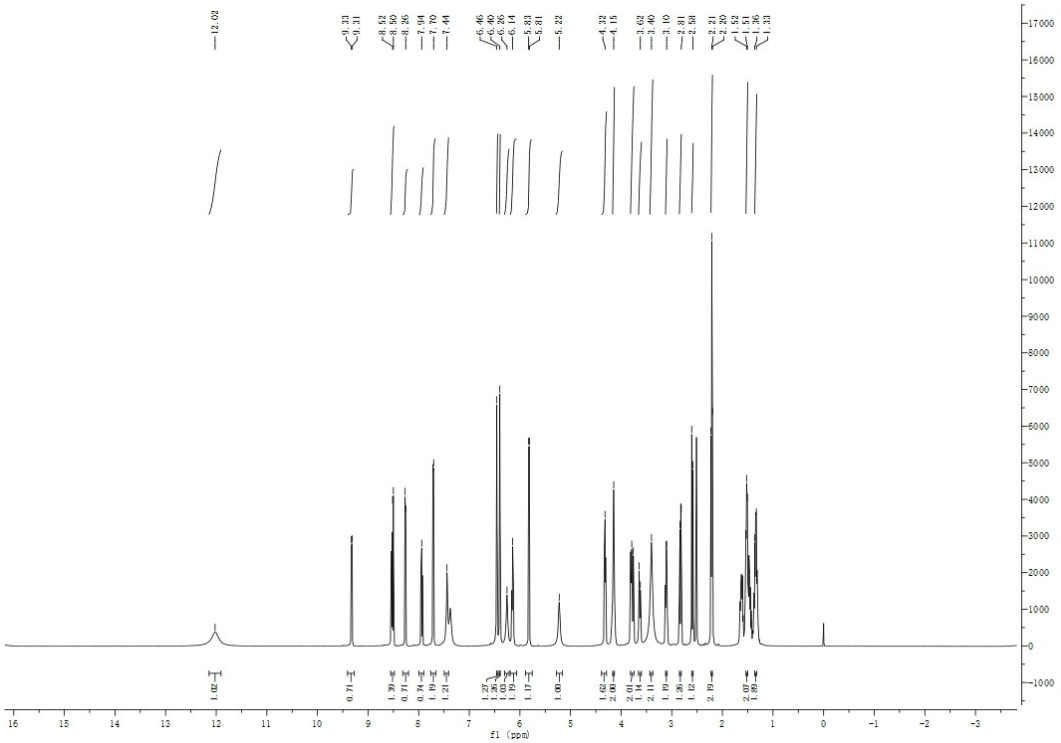



**Figure S4.** $^{1}$H NMR of compound LHX.

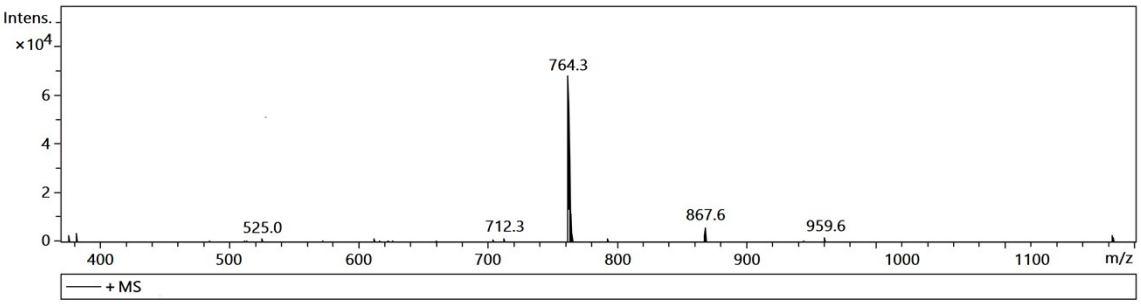



**Figure S5.** Mass spectrum of compound LHX.

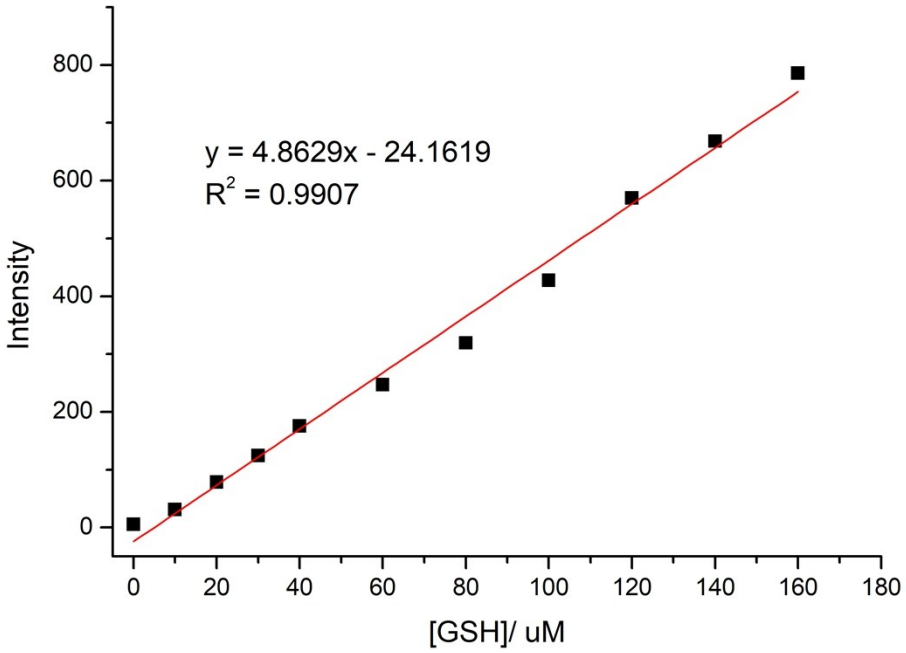



**Figure S6.** Plots of fluorescent intensity of LHX as a function of GSH concentrations.

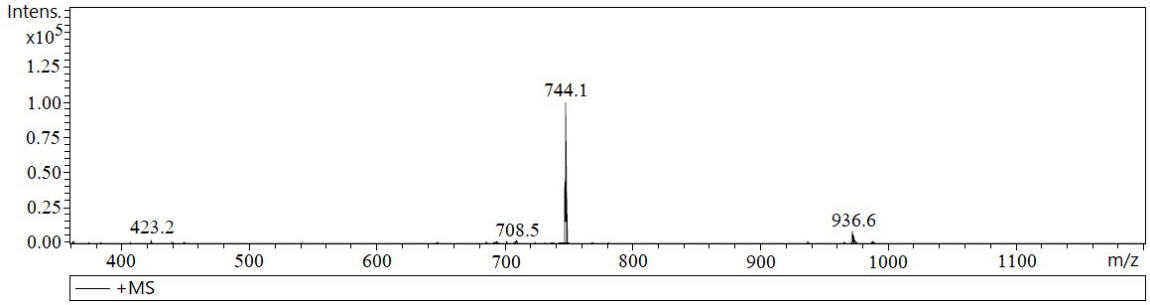



**Figure S7**. Mass spectrum of the product.

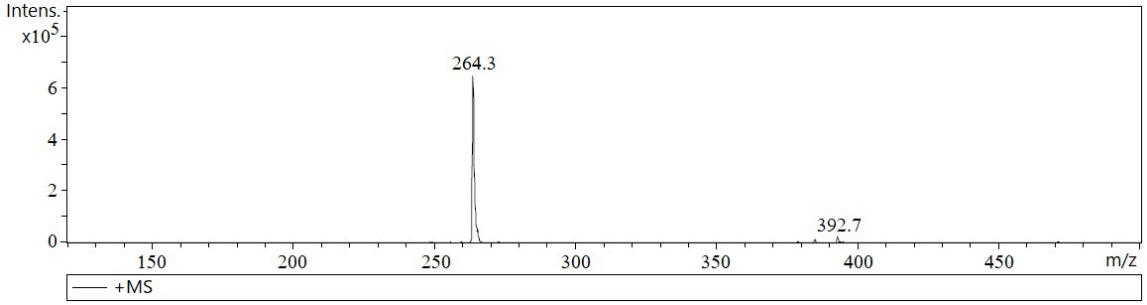



**Figure S8**. Mass spectrum of the gemcitabine.

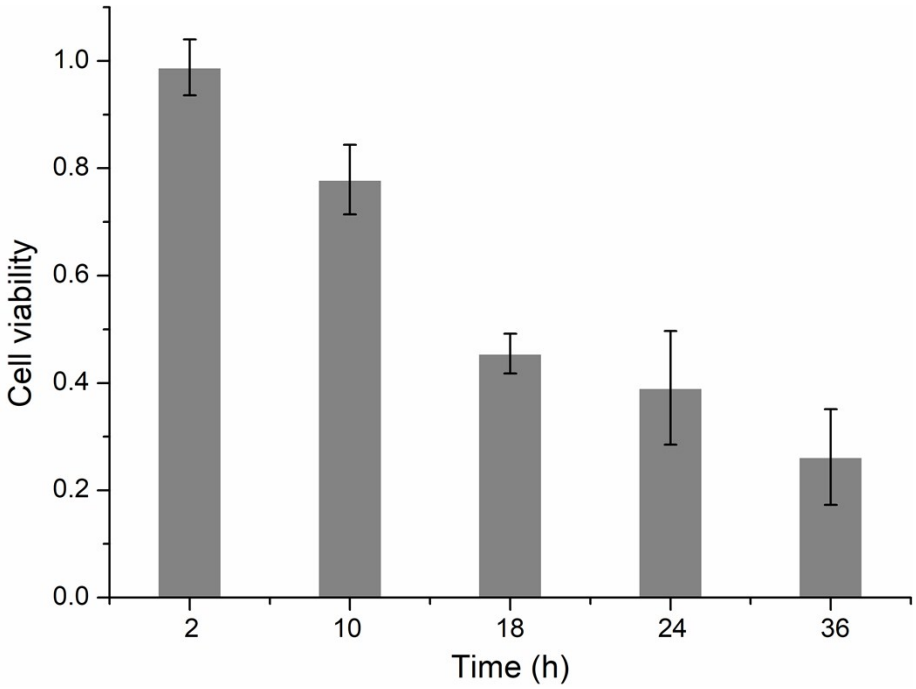



**Figure S9**. Time-dependent viability of HeLa cells treated with LHX (5.0 μM in PBS pH = 7.4).