

Figure 1 Structures of representative non-charged crosslinkers (PRIOR ART)

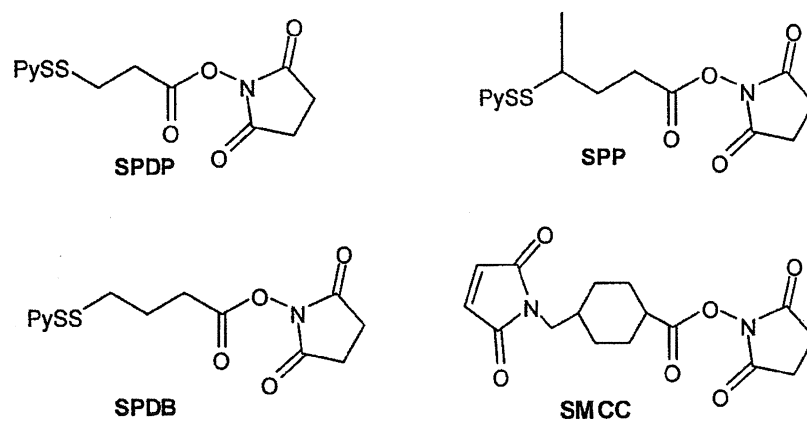


Figure 2. Structure of sulfo-SPDB and Antibody-Drug conjugate

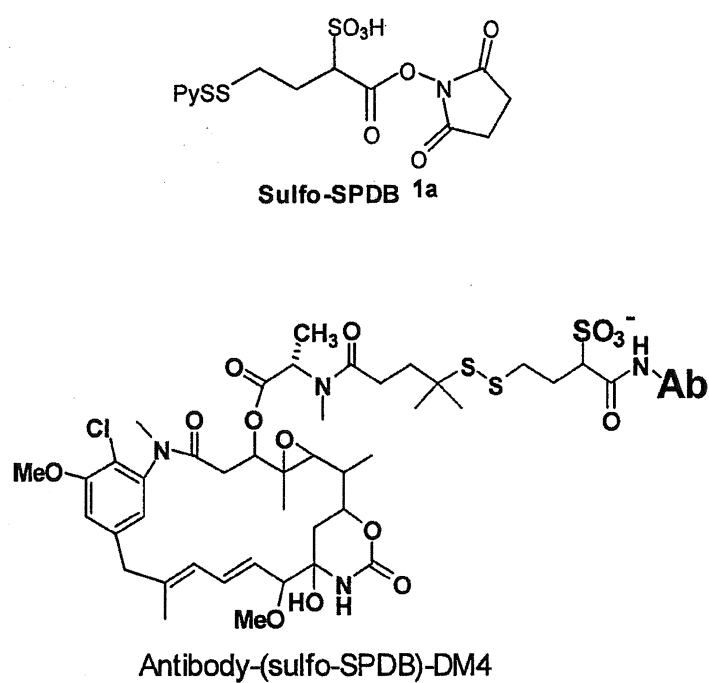
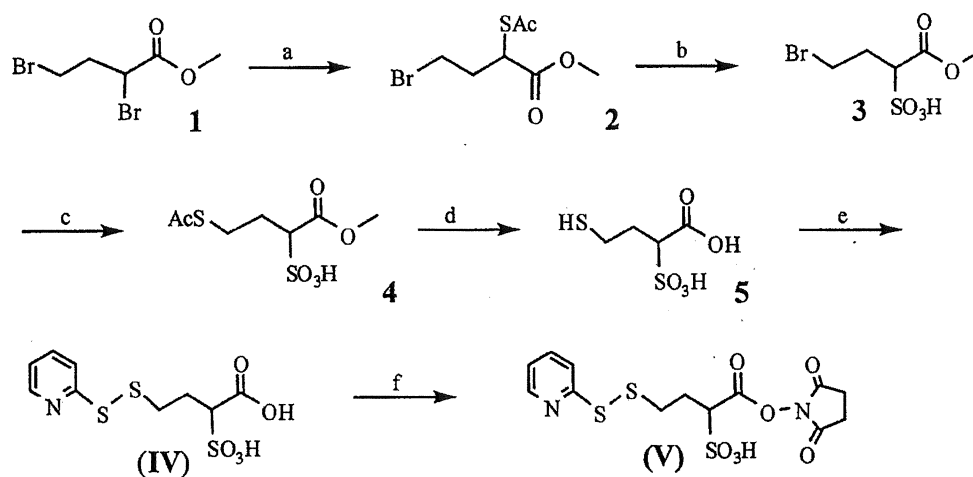


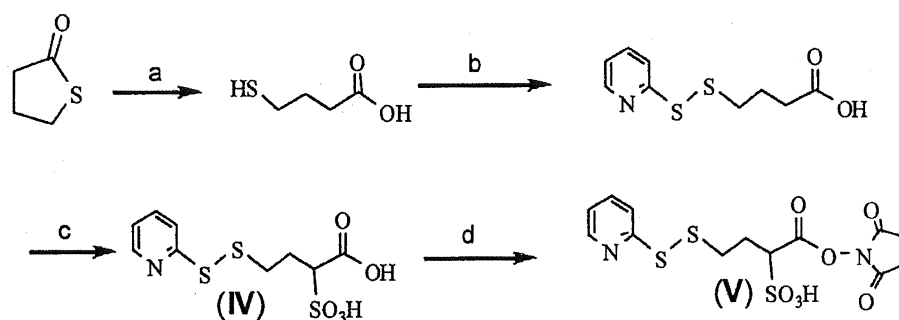
Figure 3 Synthesis of sulfo-SPDB (PRIOR ART)



Conditions: (a) HSAC, DIPEA, THF, -20°C (b) H₂O₂/HOAc; (c) HSAC, DIPEA, DMA;
 (d) NaOH; (e) (SPy)₂, pH 7.5; (f) NHS, EDC, DMA, 82%;

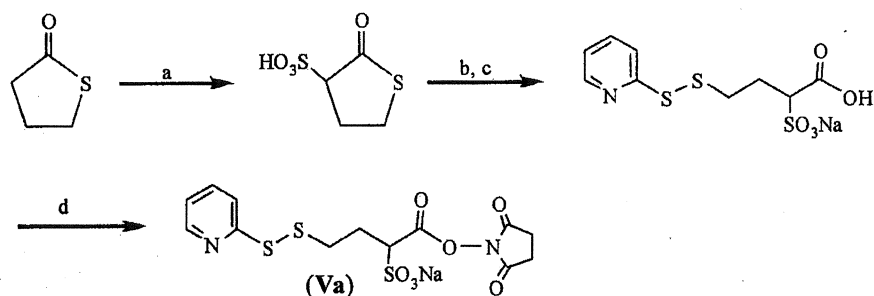
Figure 4. New synthesis of sulfo-SPDB

a)



Conditions: (a) NaOH ; (b) PySSPy; (c) ClSO₃H, ClCH₂CH₂Cl +/- base
(d) NHS, EDC

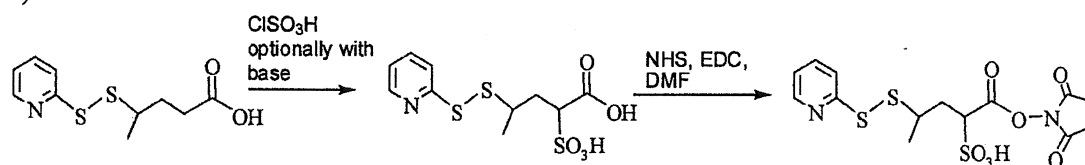
b)



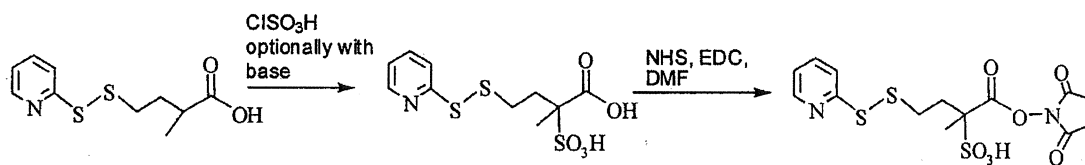
Conditions: (a) ClSO₃H/DIPEA; (b) 0.5 M NaOH; (c) pH 7, PySSPy;
(d) NHS, EDC, DMA

Figure 5. Synthesis of disulfide-containing crosslinking agents

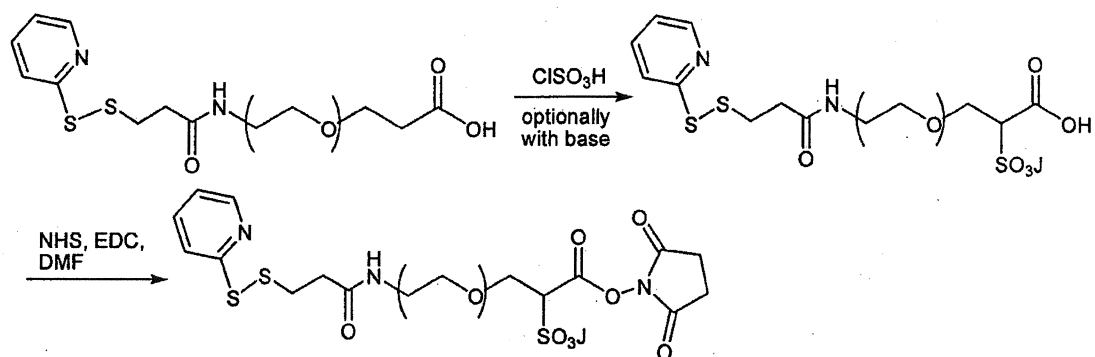
a)



b)

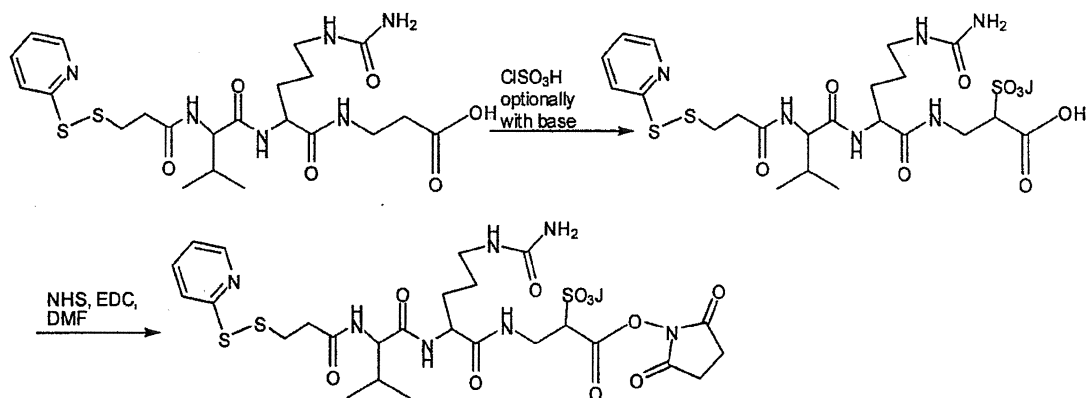


c)



Continuation of Figure 5

d)



e)

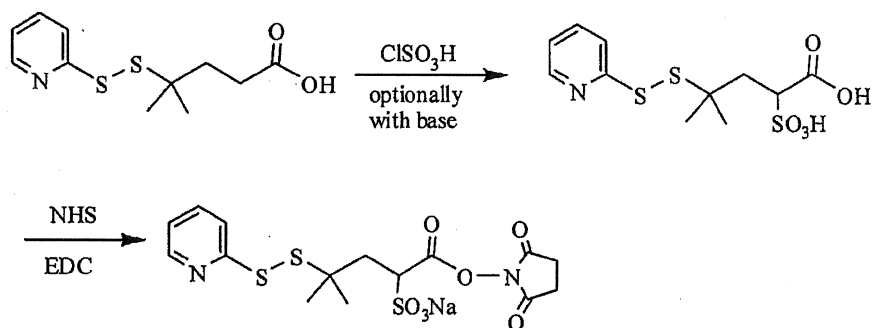
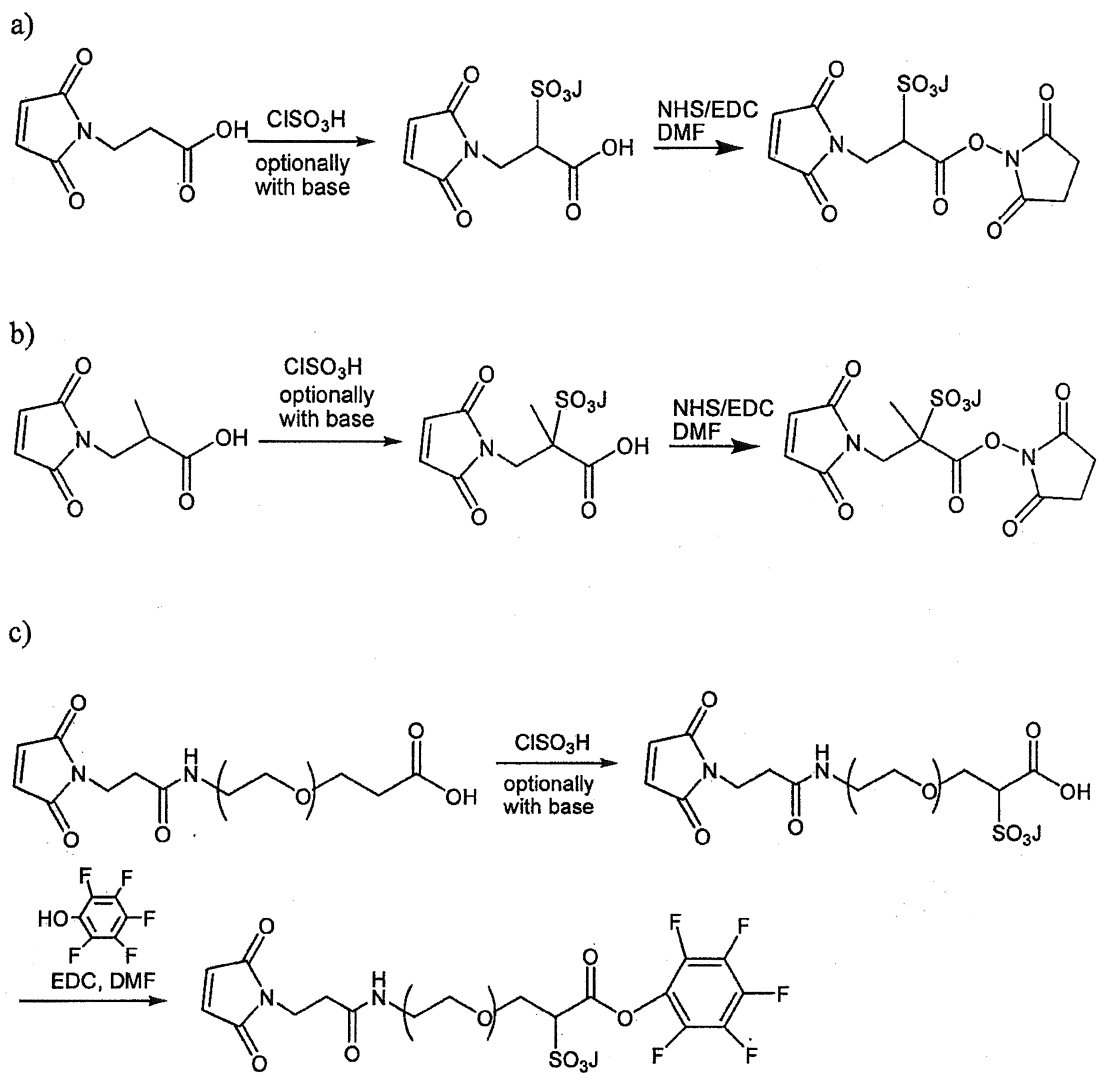


Figure 6. Synthesis of maleimide-based cross linking agents.



Continuation of Figure 6

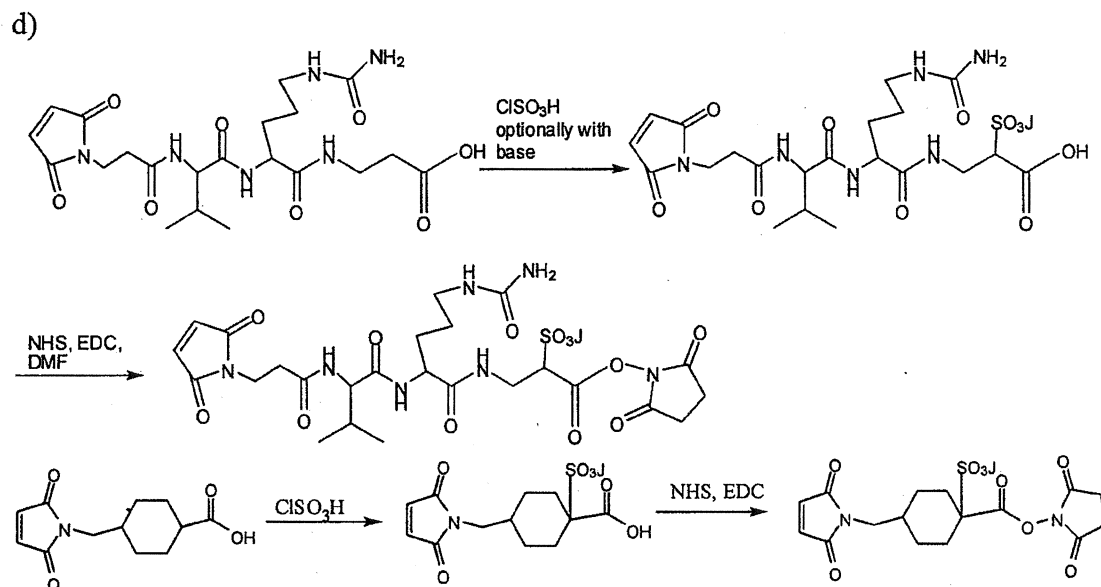
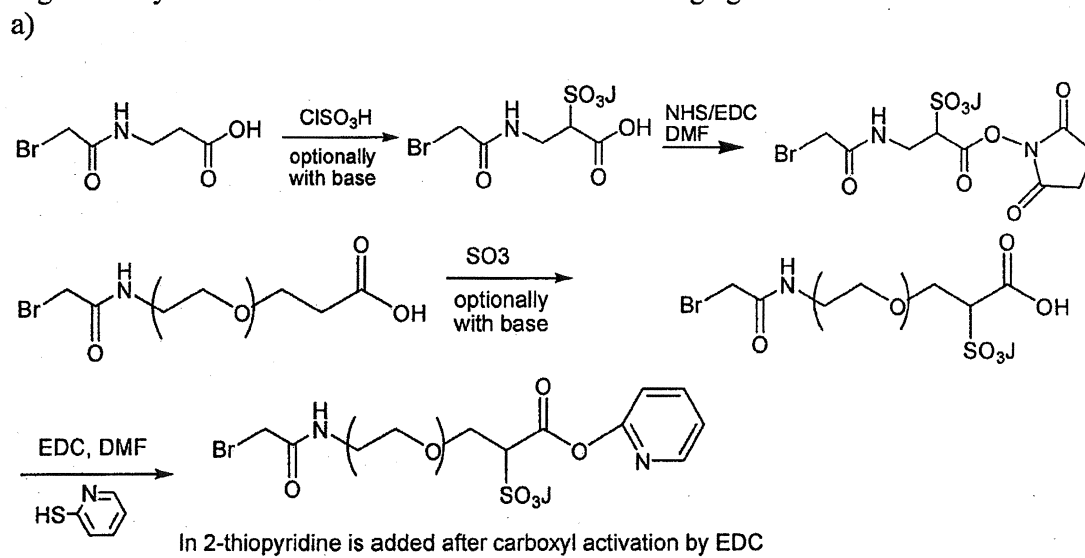


Figure 7. Synthesis of haloacetamido-based crosslinking agents



Continuation of Figure 7

b)

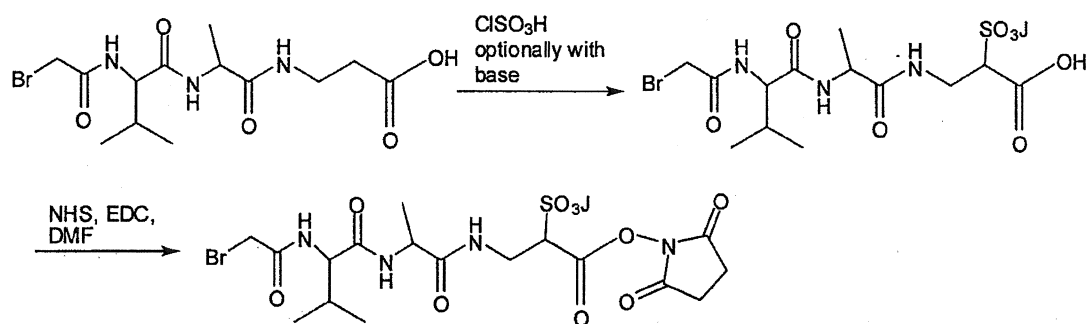


Figure 8.

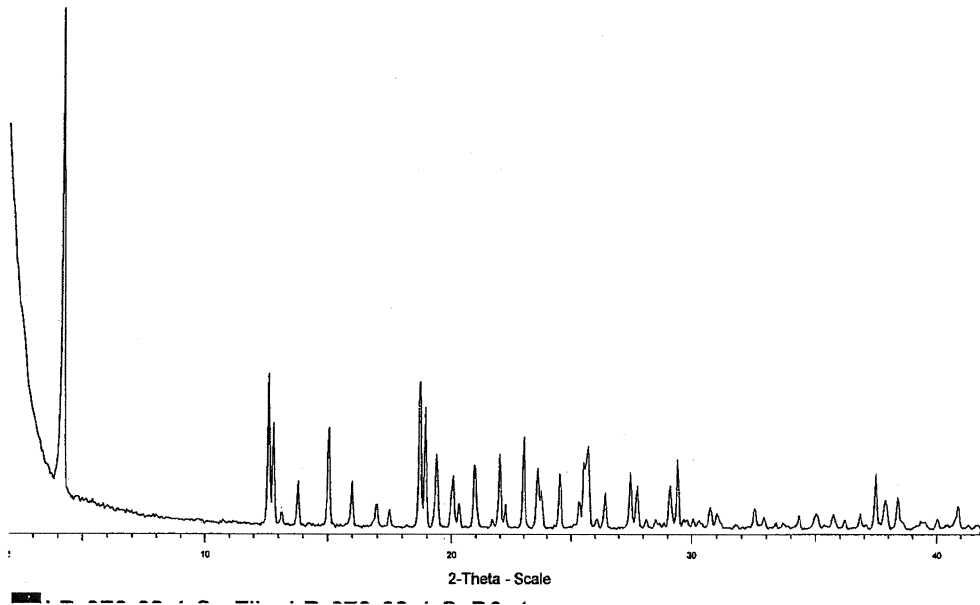


Figure 9.

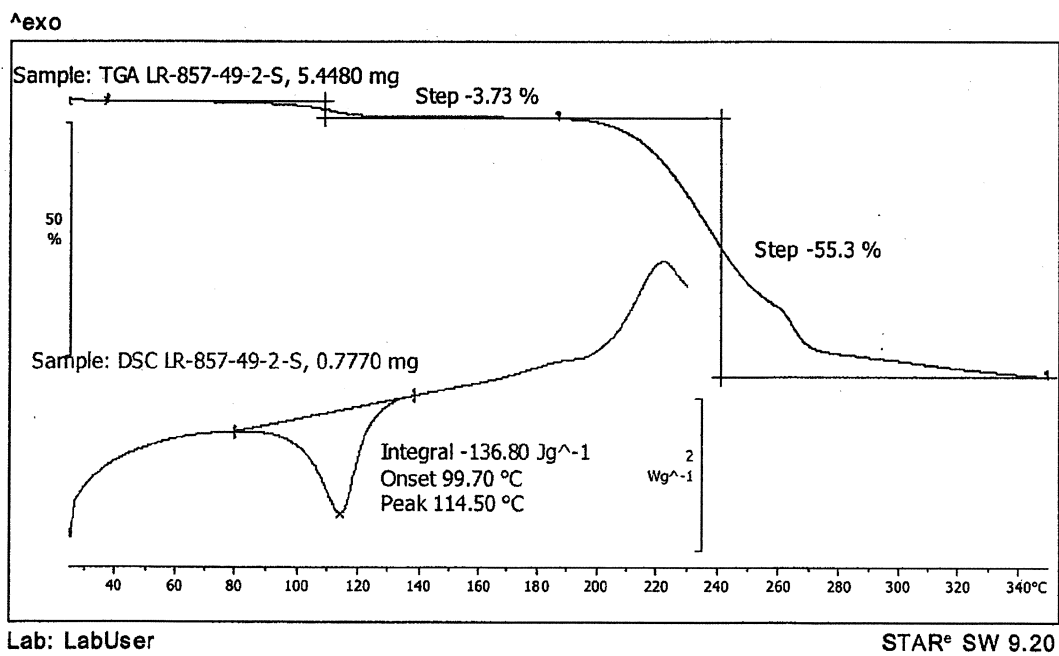


Figure 10.

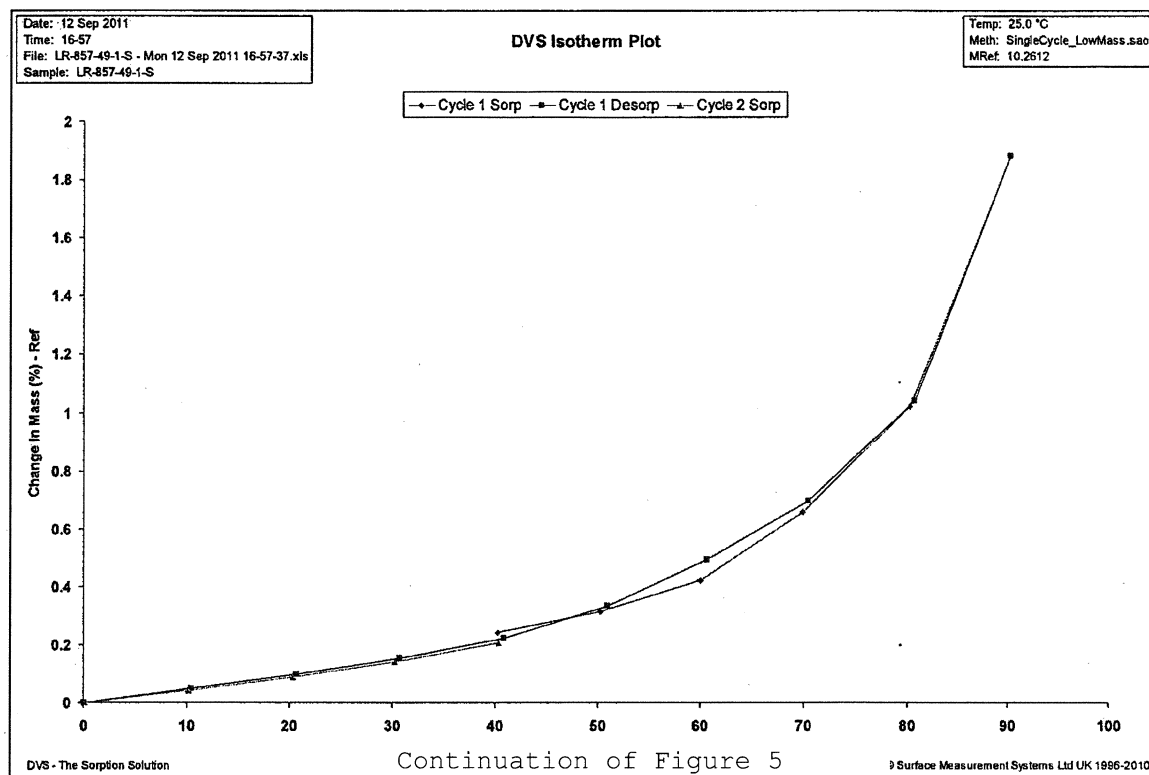


Figure 11.

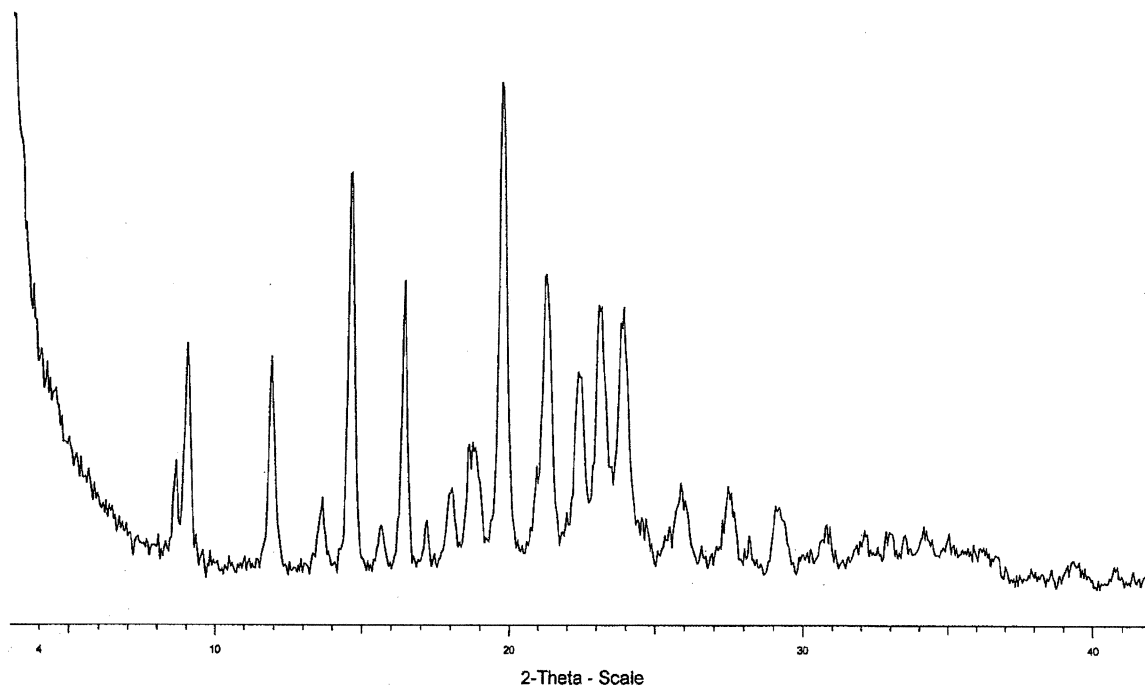


Figure 12.

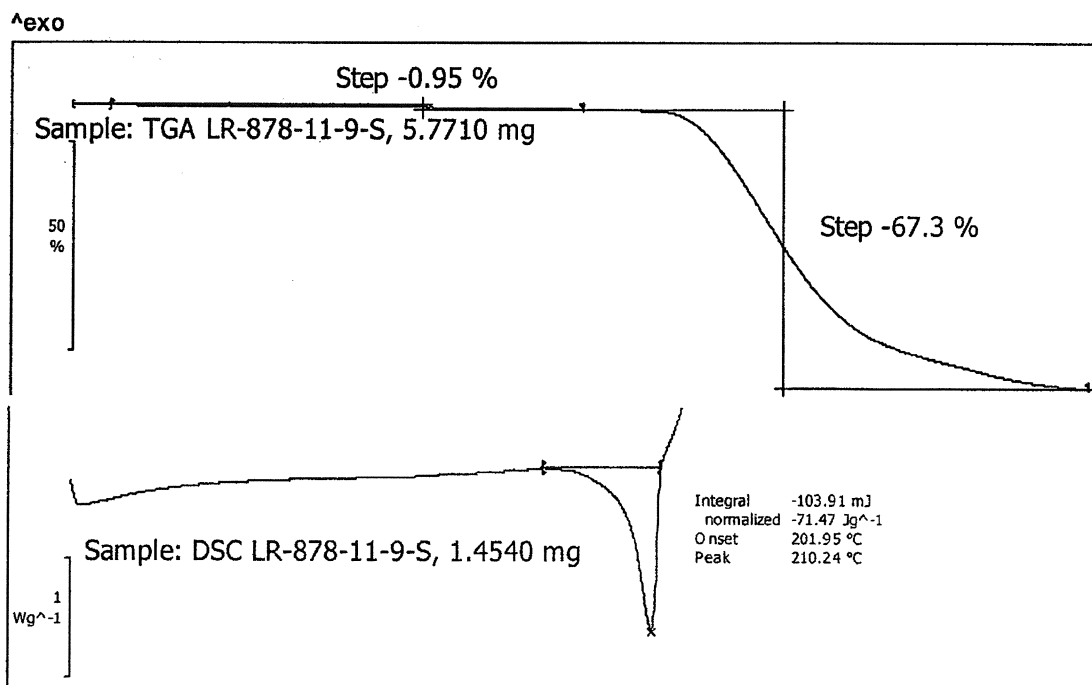


Figure 13

