Fig. 1 presents the chemical structure of a tri-antennary N-actylgalactosamine ligand.

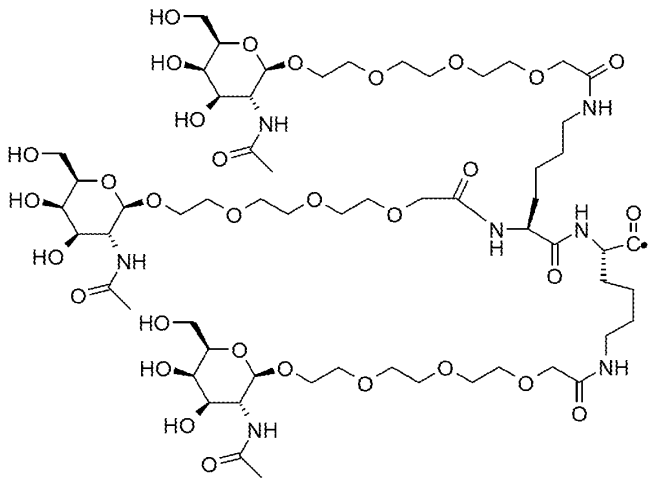


Fig. 2 presents a schematic of a synthesis of an FVII-ApoB heterodimer (XD-05311), which is discussed in connection with Example 9.

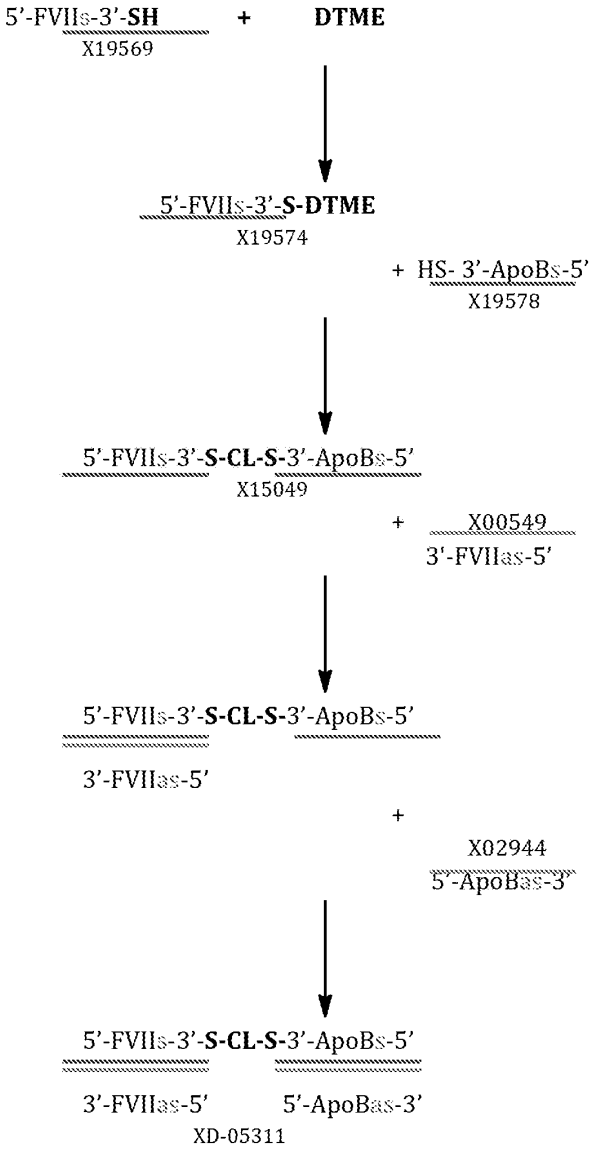


Fig. 3 presents data showing FVII activity from mouse serum *in vivo*, which is discussed in connection with Example 10.

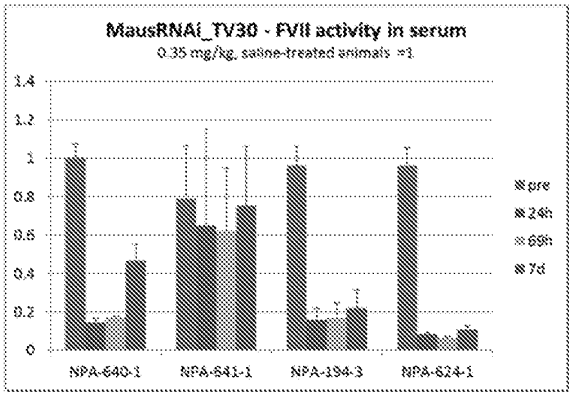


Fig. 4 presents data showing FVII and ApoB mRNA level from liver tissue in animal experiment MausRNAi-TV30, which is discussed in connection with Example 10.

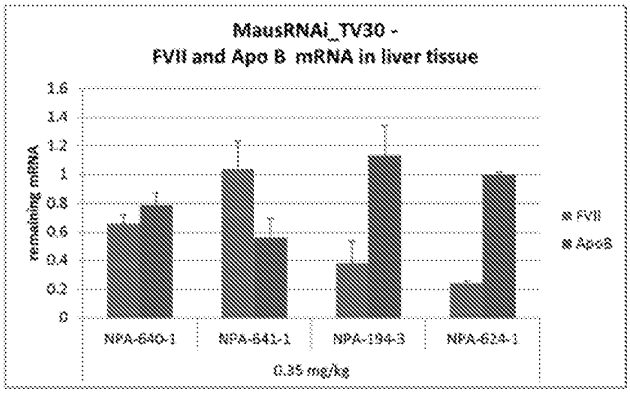


Fig. 5 presents a 5'-GalNAc-FVII canonical control, which is discussed in connection with Example 11.

GalNAc

|

3'-FVIIs-5'

5'-FVIIas-3'

Fig. 6 presents a GalNAc-homodimer conjugate (XD-06330), which is discussed in connection with Example 12.

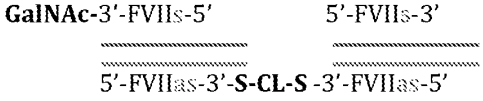


Fig. 7 presents a schematic of a synthesis of a GalNAc-homodimer conjugate (XD-06360), which is discussed in connection with Example 13.

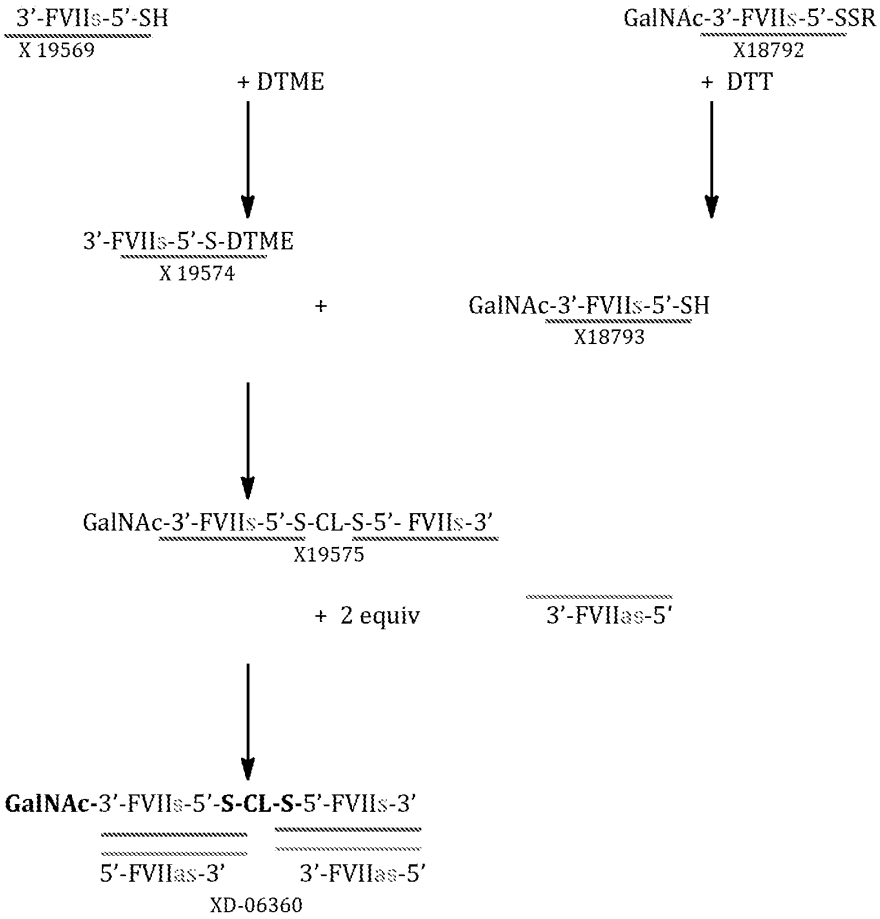


Fig. 8 presents a schematic of a synthesis of a GalNAc-homodimer conjugate (XD-06329), which is discussed in connection with Example 14.

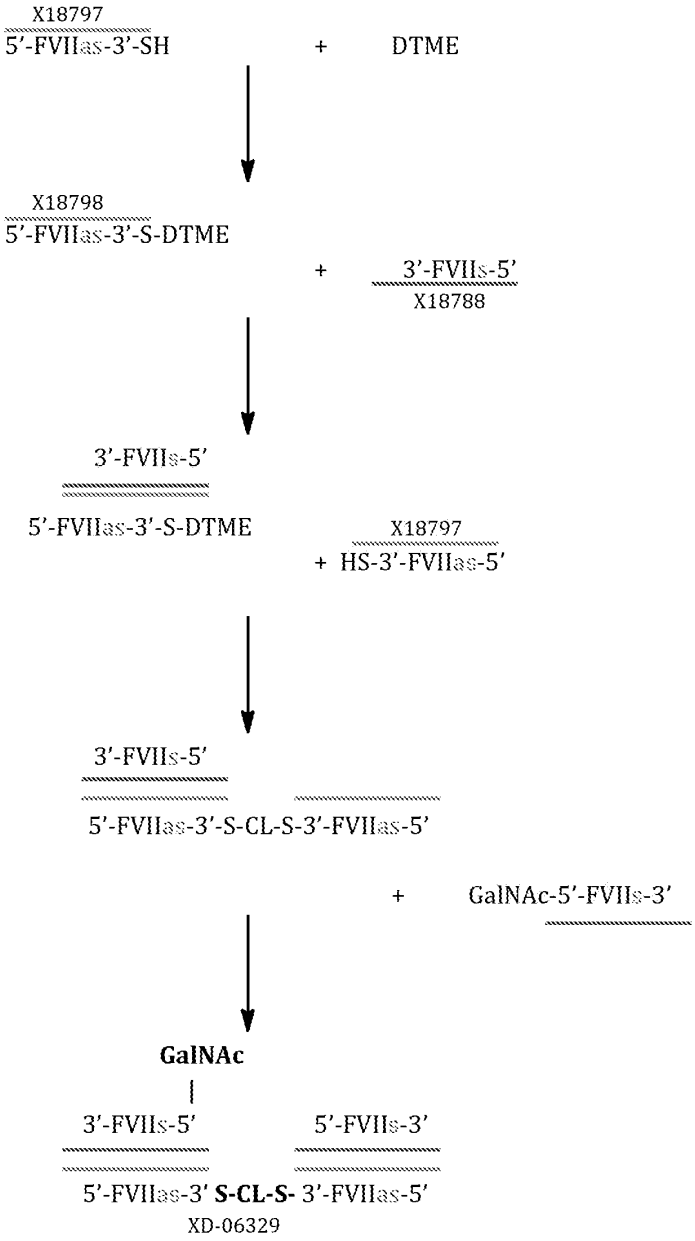
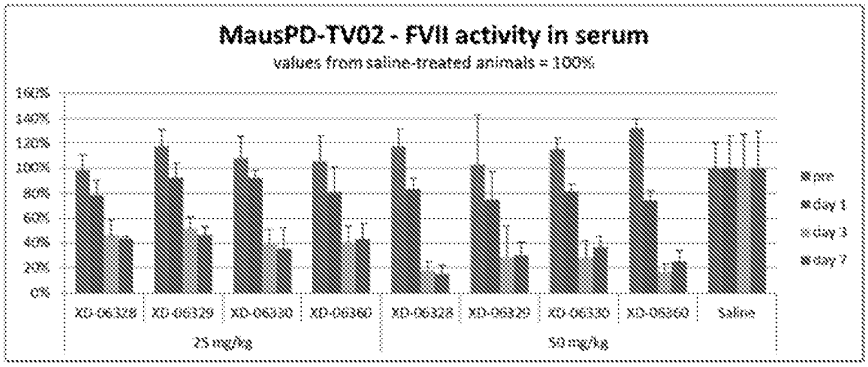


Fig. 9 presents data showing FVII activity in mouse serum (knockdown by FVII homodimeric GalNAc conjugates), which is discussed in connection with Example 15.



Figs. 10A and 10B and 10C presents data showing FVII activity in mouse serum (knockdown by FVII homodimeric GalNAc conjugates normalized for GalNAc content), which is discussed in connection with Example 15.

Fig. 10A

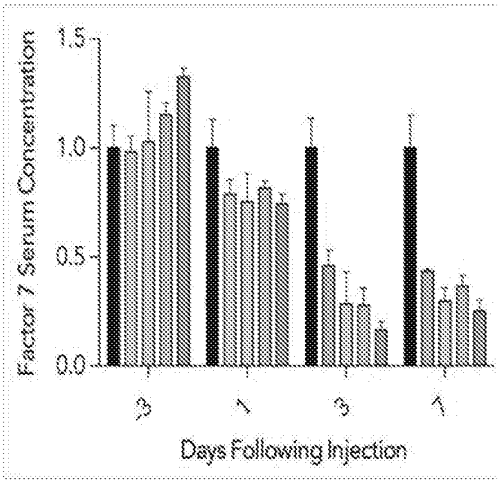


Fig. 10B

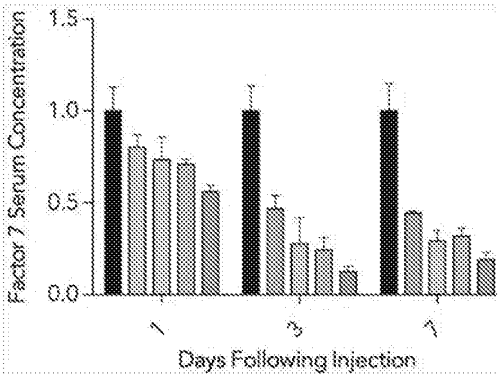


Fig. 10C

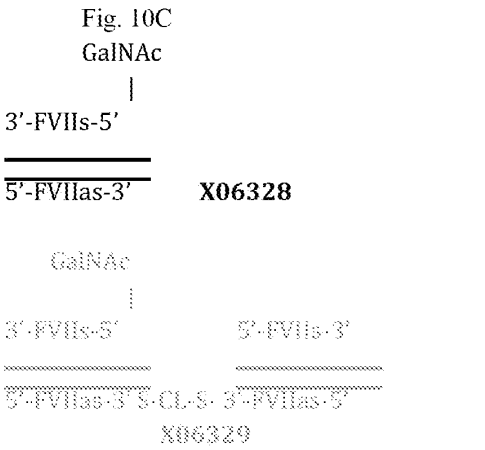
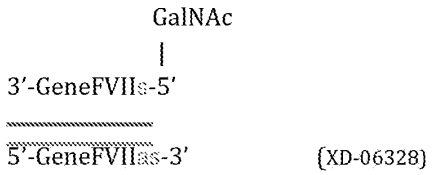
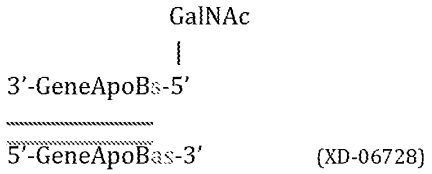


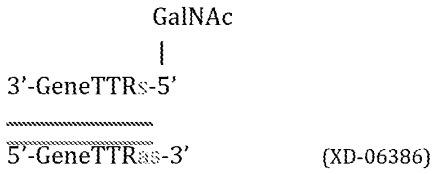
Fig. 11 presents canonical GalNAc-siRNAs independently targeting FVII, ApoB and TTR, which are discussed in connection with Example 16.



(XD-06328)



(XD-06728)



(XD-06386)

Fig.12 presents a GalNAC-heterotrimer conjugate (XD06726), which is discussed in connection with Example 17. Key: In this example, "GeneA" is siFVII; "GeneB" is siApoB; and "GeneC" is siTTR.

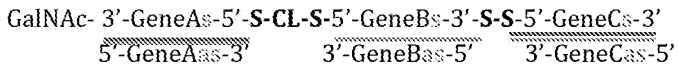


Fig. 13 presents a schematic of a synthesis strategy for a GalNAc-conjugated heterotrimer (XD06726), which is discussed in connection with Example 17. Key: In this example, "GeneA" is siFVII; "GeneB" is siApoB; and "GeneC" is siTTR.

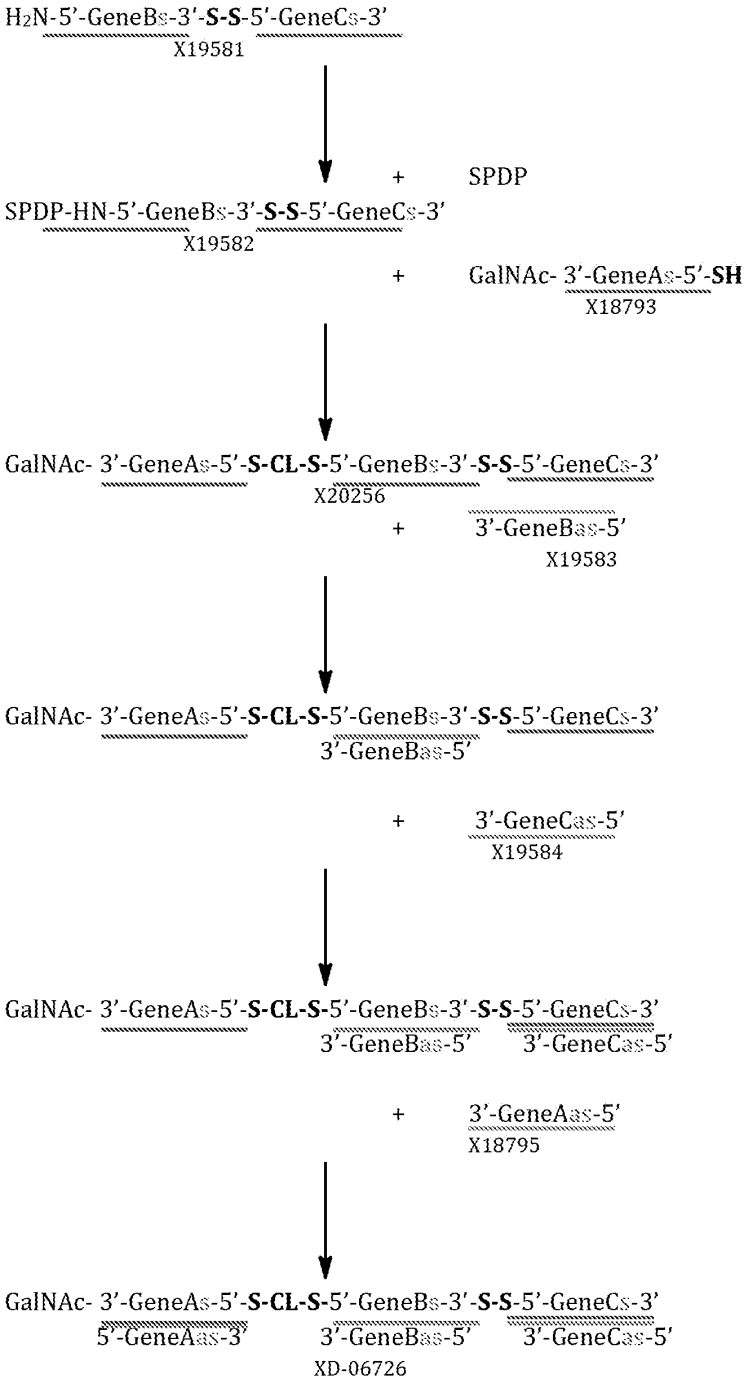
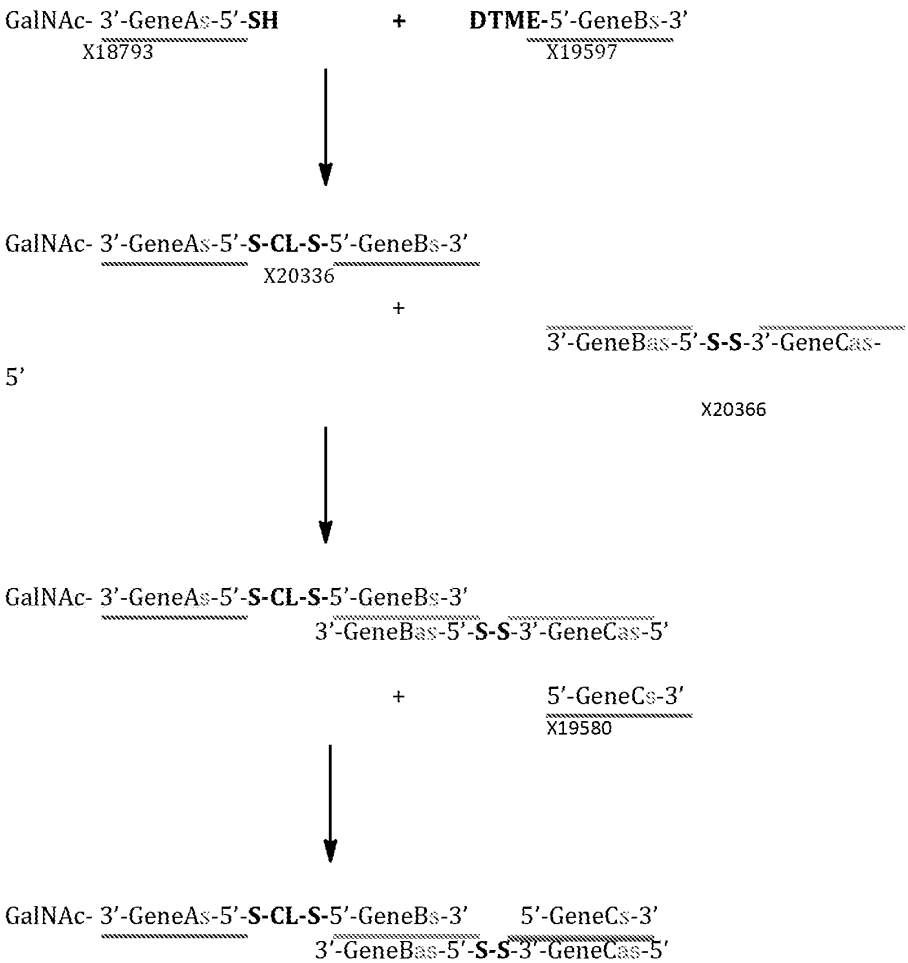


Fig. 14 presents a GalNAc-heterotrimer conjugate (XD06727), which is discussed in connection with Example 18. Key: In this example, "GeneA" is siFVII; "GeneB" is siApoB; and "GeneC" is siTTR.

GalNAc- 3'-GeneAs-5'-**S-CL-S**-5'-GeneBs-3' 5'-GeneCs-3'
5'-GeneAas-3' 3'-GeneBas-5'-**S-S**-3'-GeneCas-5'

Fig. 15 presents a schematic of a synthesis strategy for GalNAc-Conjugated Heterotrimer (XD06727), which is discussed in connection with Example 18. Key: In this example, "GeneA" is siFVII; "GeneB" is siApoB; and "GeneC" is siTTR.



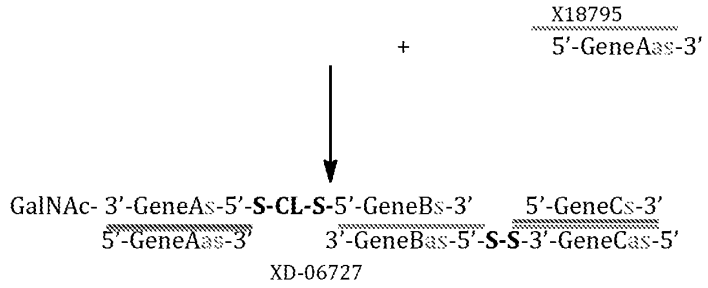

X18795
+
5'-GeneAas-3'
GalNAc- 3'-GeneAs-5'-S-CL-S-5'-GeneBs-3'
5'-GeneCs-3'
5'-GeneAas-3'
3'-GeneBas-5'-S-S-3'-GeneCas-5'
XD-06727

Fig. 16 presents data for an HPLC analysis of reaction of action of X20336 to X20366, which is discussed in connection with Example 18.

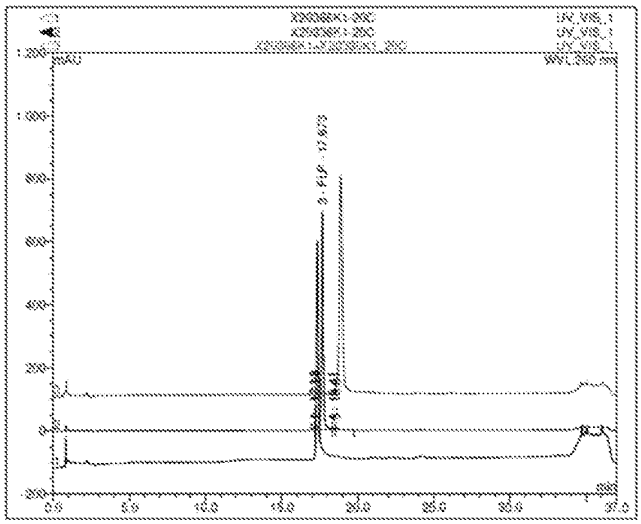


Fig. 17 presents data for an HPLC analysis of addition of X19580 to the reaction, which is discussed in connection with Example 18.

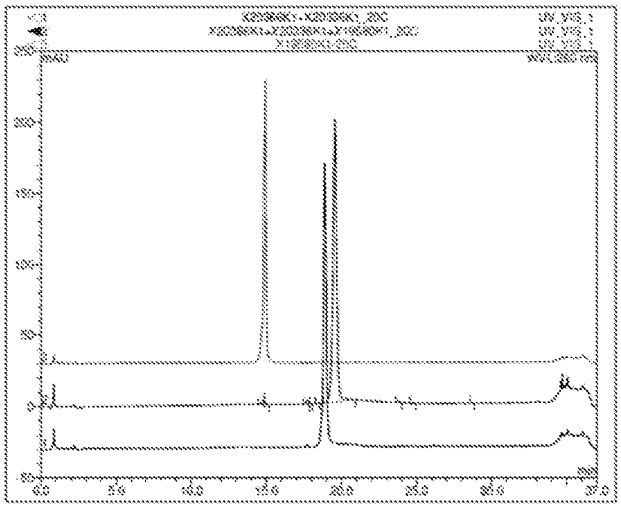
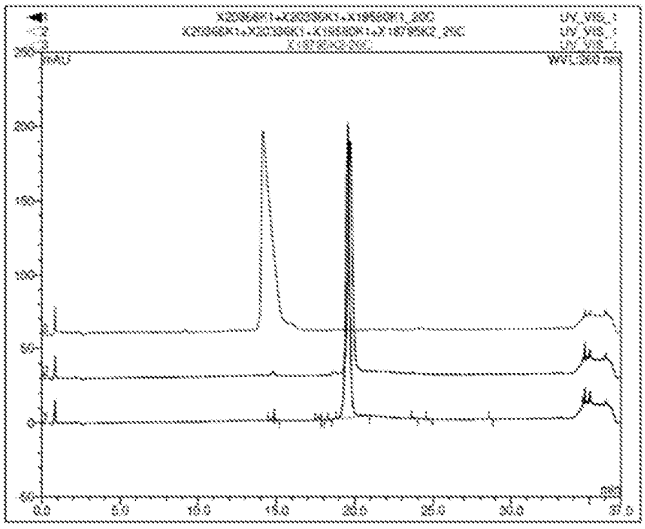


Fig. 18 presents data for an HPLC analysis of addition of X18795 (5'-siFVIIantisense-3') to reaction mixture to yield XD-06727, which is discussed in connection with Example 18.



Figs. 19A and 19B present data for TTR protein levels in serum samples (measured by ELISA), which is discussed in connection with Example 20.

Fig. 19A

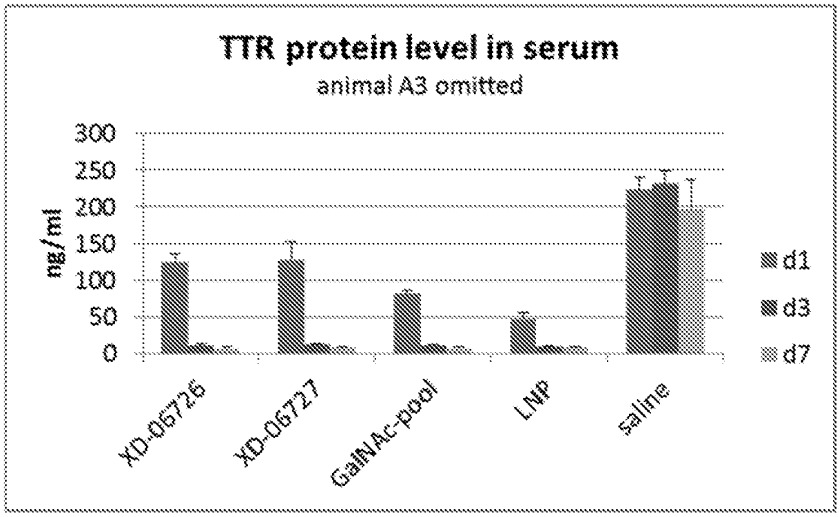
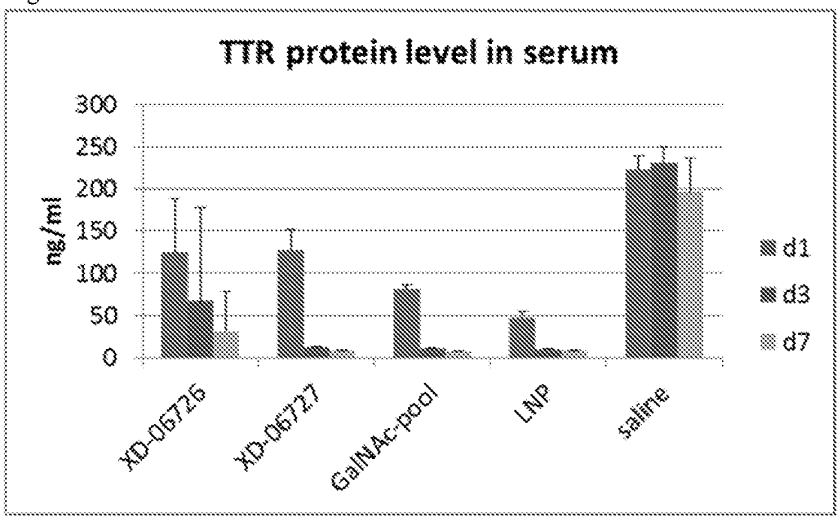


Fig. 19B



Figs. 20A and 20B present data for FVII enzymatic activity in serum samples, which is discussed in connection with Example 20.

Fig. 20A

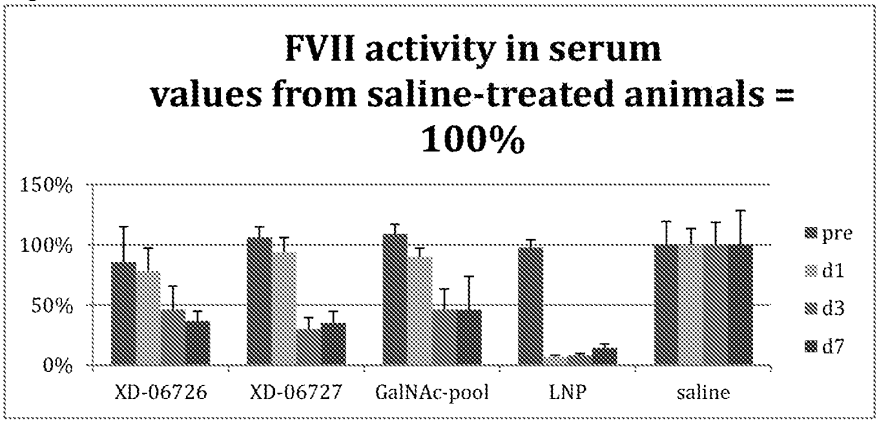
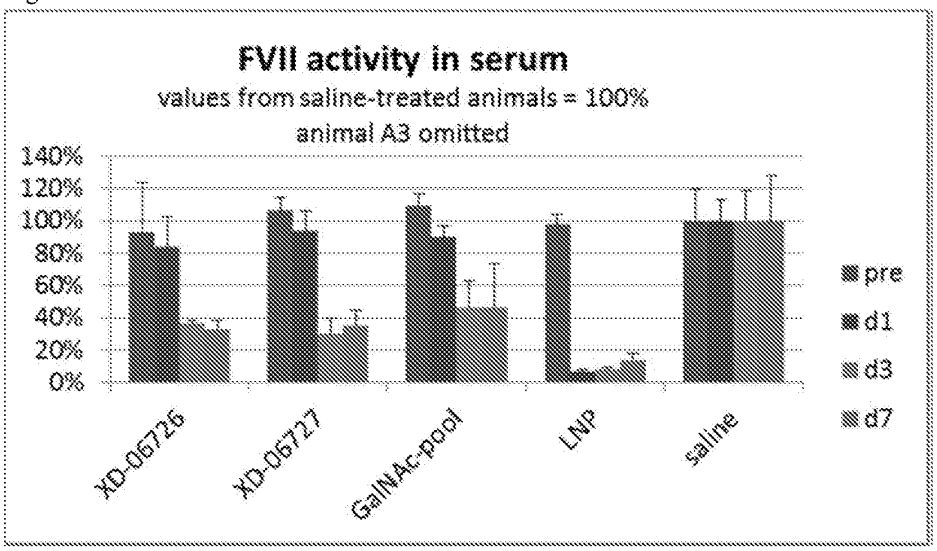


Fig. 20B



Figs. 21A and 21B present data for ApoB protein levels in serum samples (measured by ELISA), which is discussed in connection with Example 20.

Fig. 21A

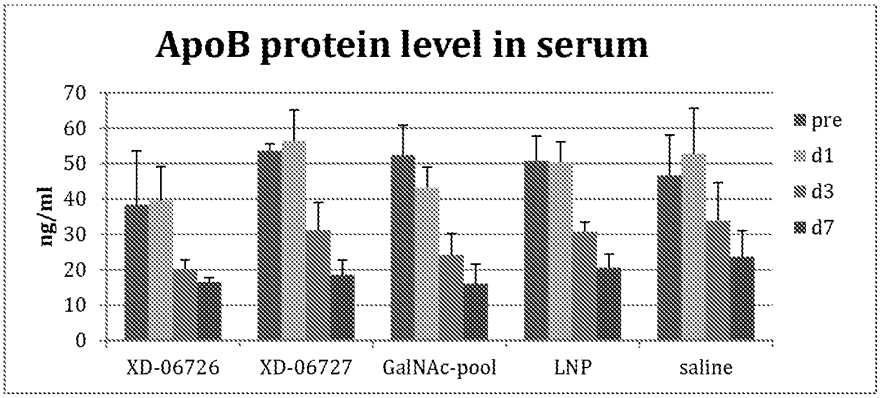
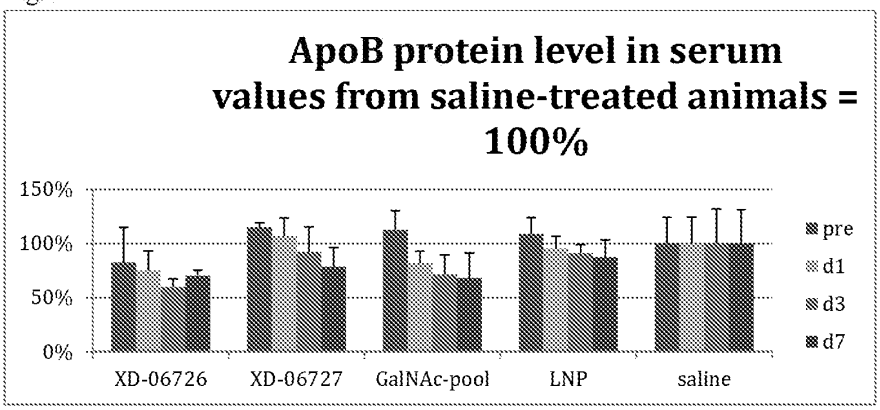


Fig. 21B



Figs. 22A and 22B present target knockdown in liver data, which is discussed in connection with Example 20.

Fig. 22A

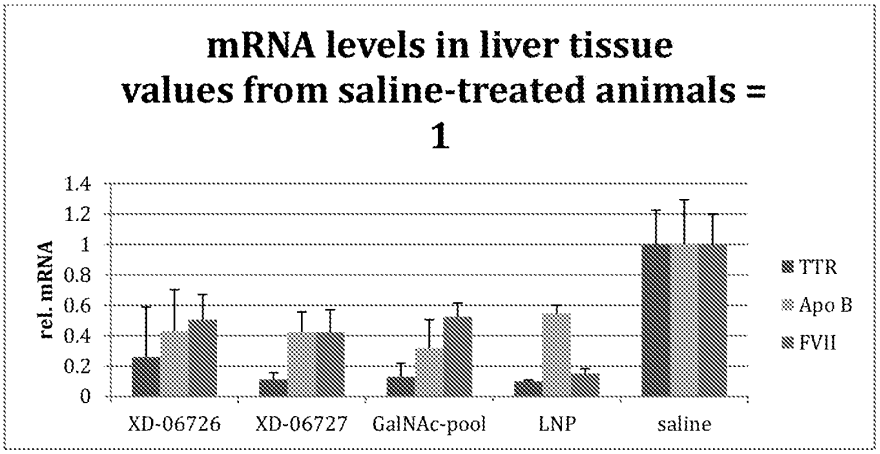


Fig. 22B

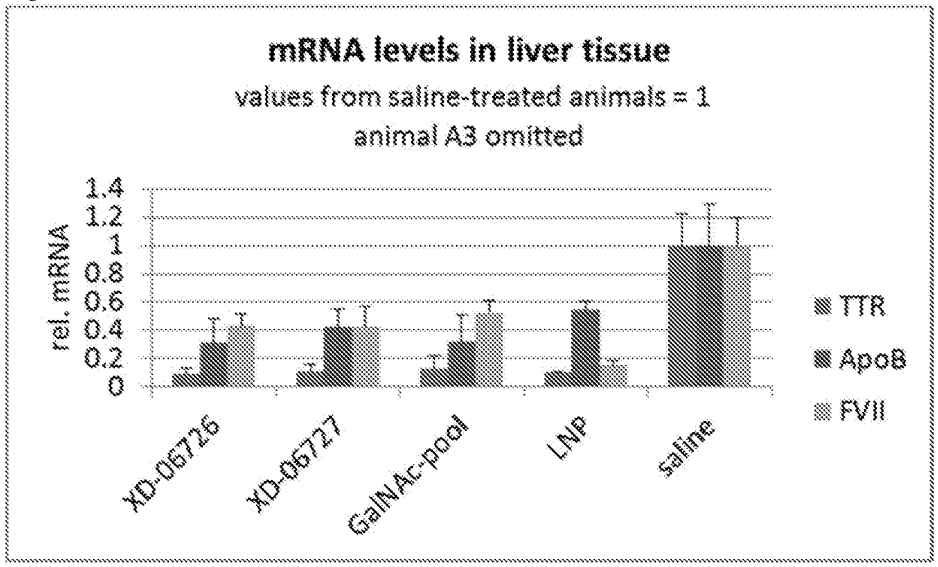


Fig. 23 presents a GalNAc-heterotetramer conjugate (XD-07140), which is discussed in connection with Example 21. Key: In this example, "GeneA" is siFVII; "GeneB" is siApoB; and "GeneC" is siTTR.

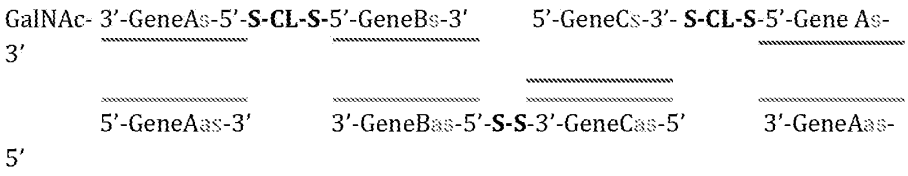
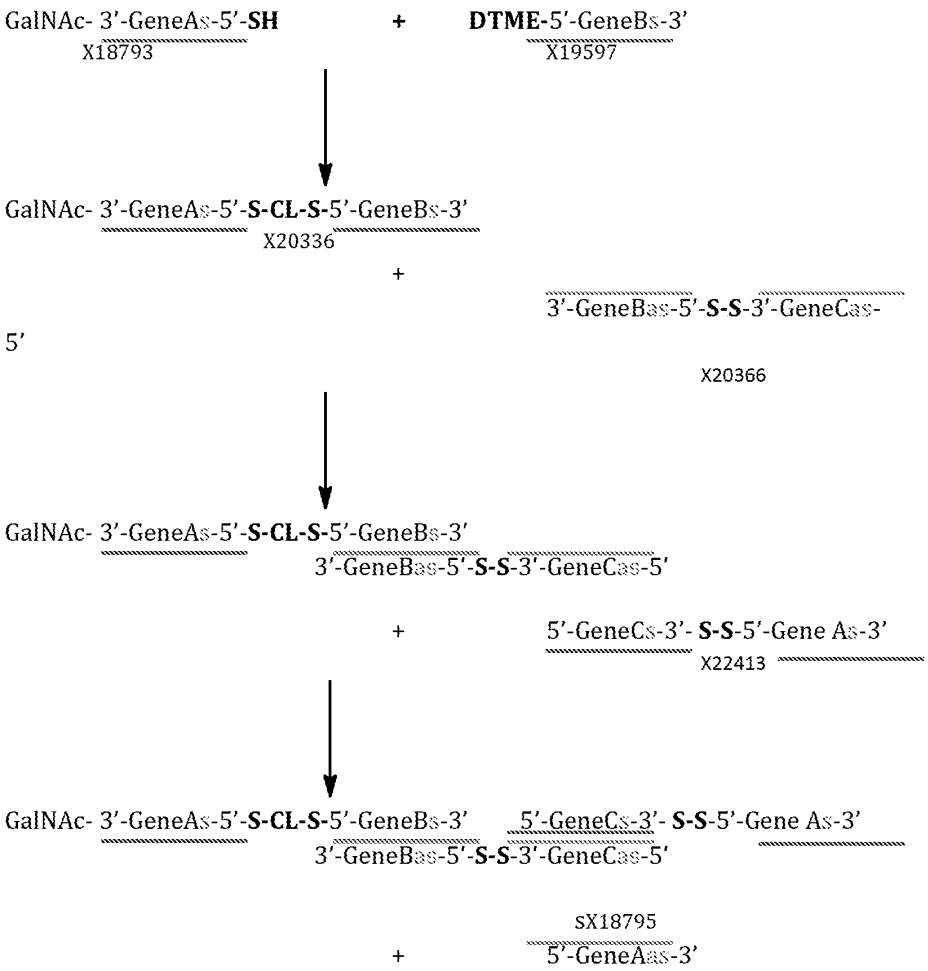


Fig. 24 presents a schematic of a synthesis of a GalNAc-heterotetramer conjugate (XD-07140), which is discussed in connection with Example 21. Key: In this example, "GeneA" is siFVII; "GeneB" is siApoB; and "GeneC" is siTTR.



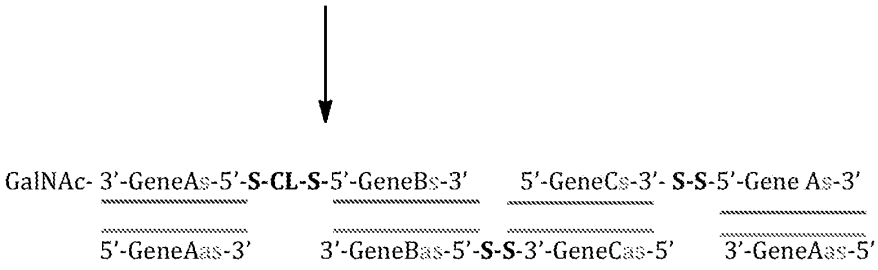


Fig 25 presents a HPLC Analysis of a GalNAc-siFVII-siApoBsiTTR-siFVII Tetramer(XD-07140), which is discussed in connection with Example 21.

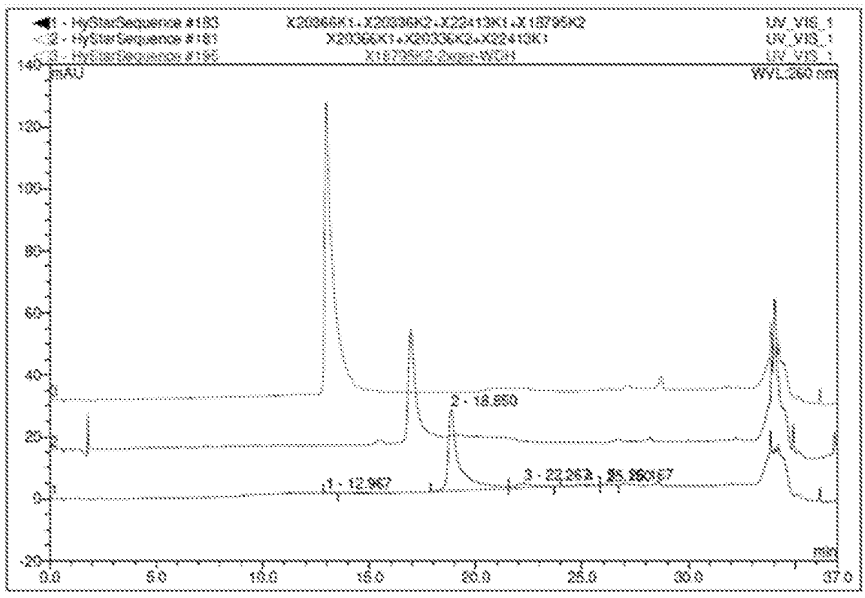


Fig. 26 presents a synthesis of a homodimer, which is discussed in connection with Example 22.

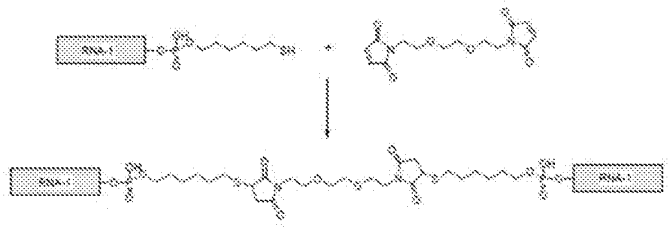


Fig. 27 presents an SEC HPLC analysis of XD-05305, which is discussed in connection with Example 22.

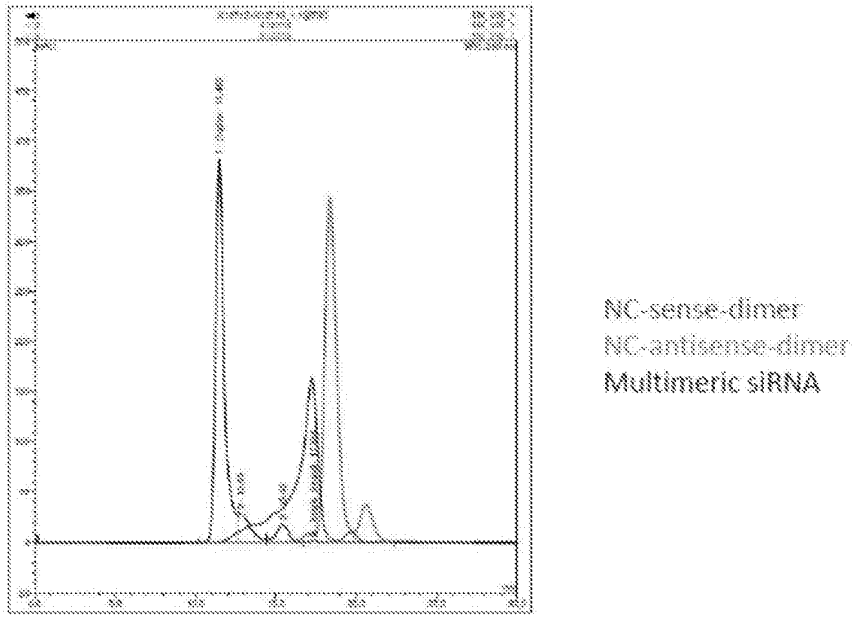
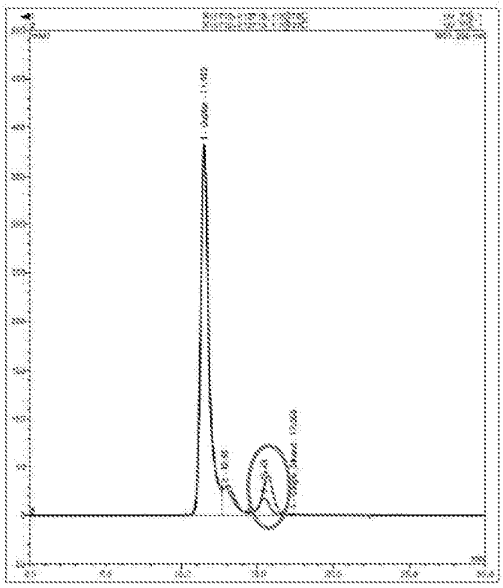
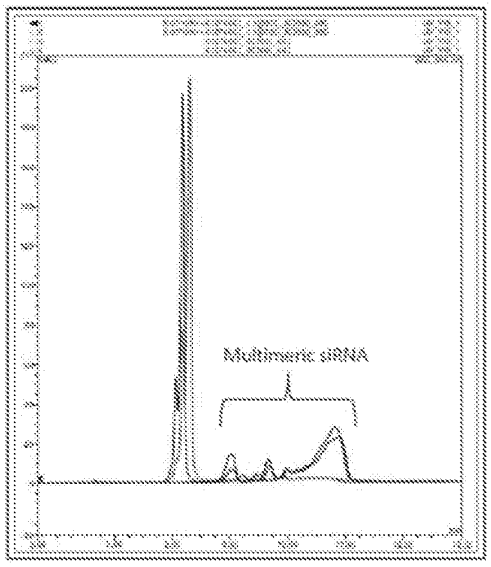


Fig. 28 presents an SEC HPLC Analysis of XD-05305, which is discussed in connection with Example 22.



Axolabs' conditions
Park's conditions

Fig 29 presents an IEX HPLC analysis of XD-05305, which is discussed in connection with Example 22.



NC-sense-dimer
NC-antisense-dimer
Axolabs' annealing conditions
Park's annealing conditions

Fig. 30 presents an SEC HPLC analysis of XD-05305, which is discussed in connection with Example 22. Multimeric siRNA is the left-hand peak; dimeric siRNA is the middle peak; and canonical siRNA is the right-hand peak.

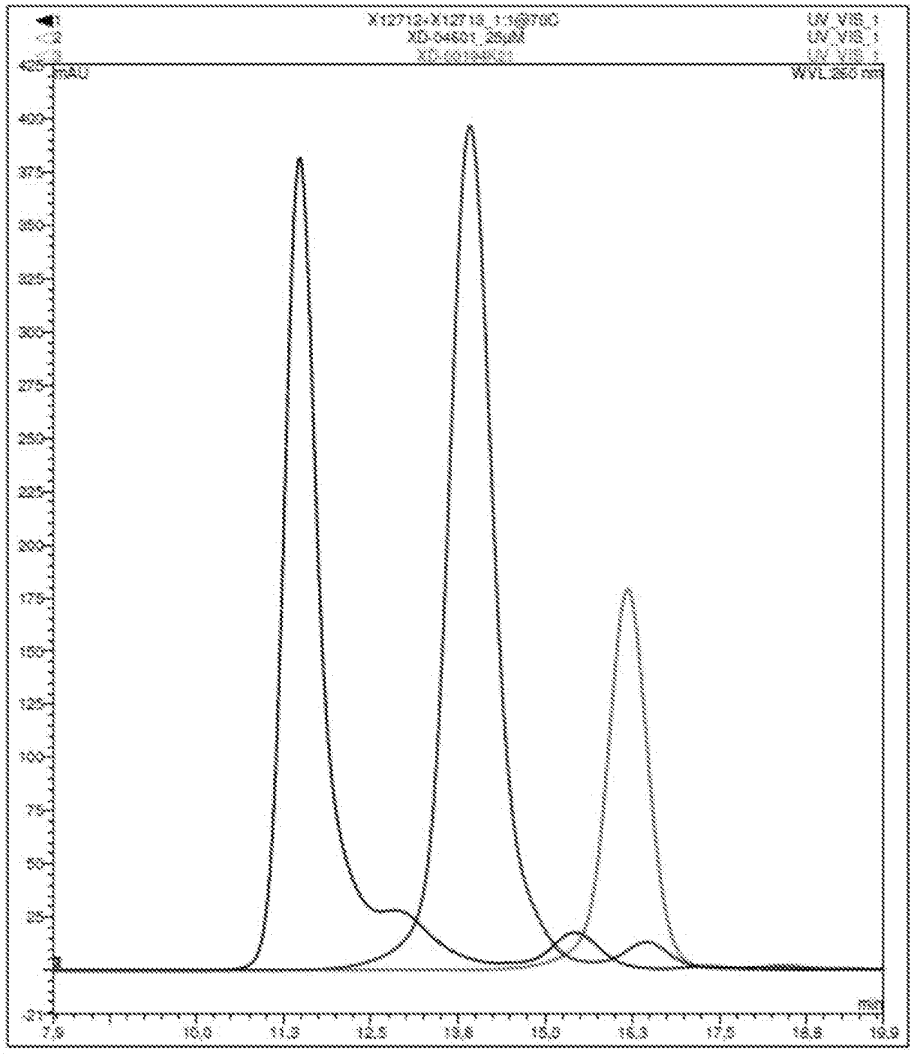


Fig. 31 presents the effect of salt concentration and reaction temperature on a multimeric siRNA mixture, which is discussed in connection with Example 22.

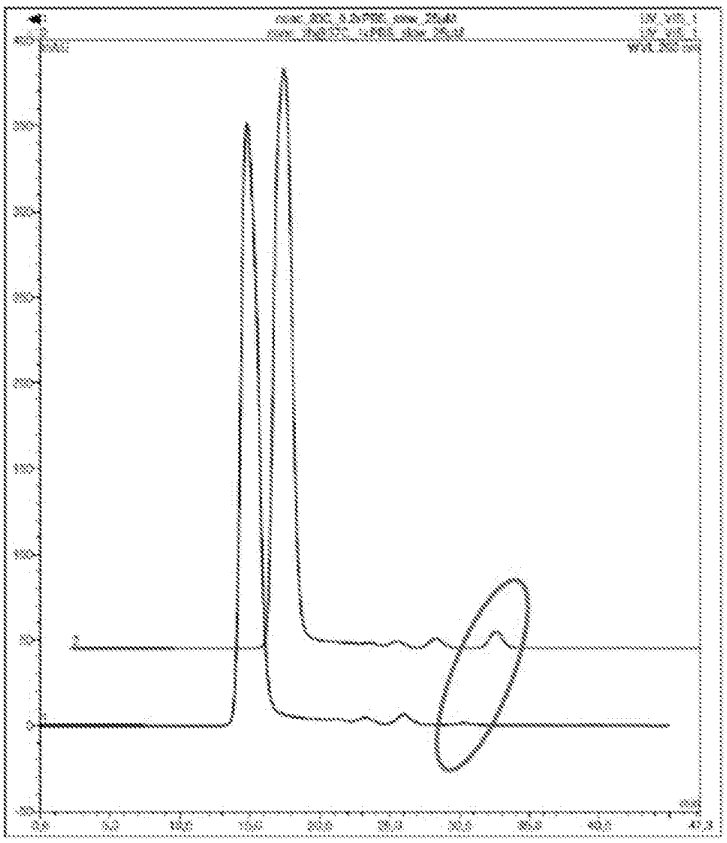


Fig. 32 presents data showing that the higher the concentration of termination strand (in this case, the antisense strand was used as the terminator), the smaller the multimerized siRNA fraction. The data is discussed in connection with Example 22.

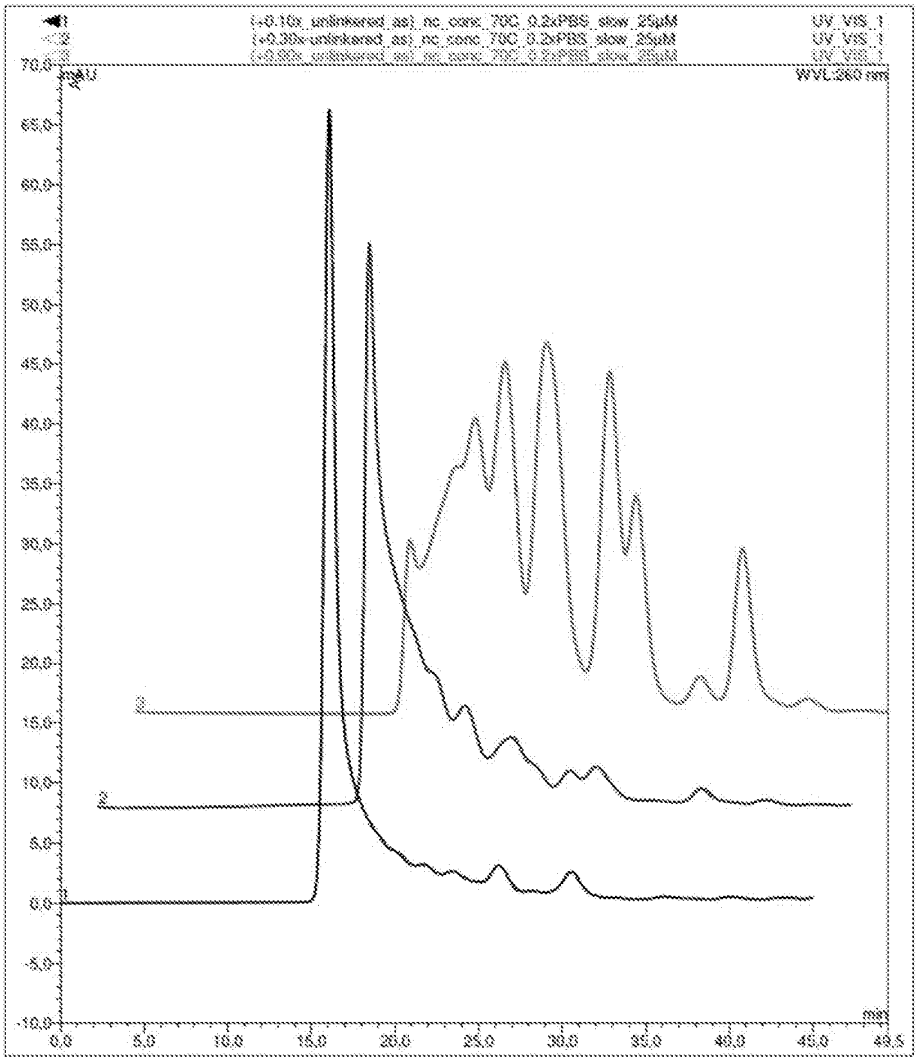


Fig. 33 presents data showing that the smaller the concentration of sense homodimer, the smaller the multimerized siRNA fraction. The data is discussed in connection with Example 22.

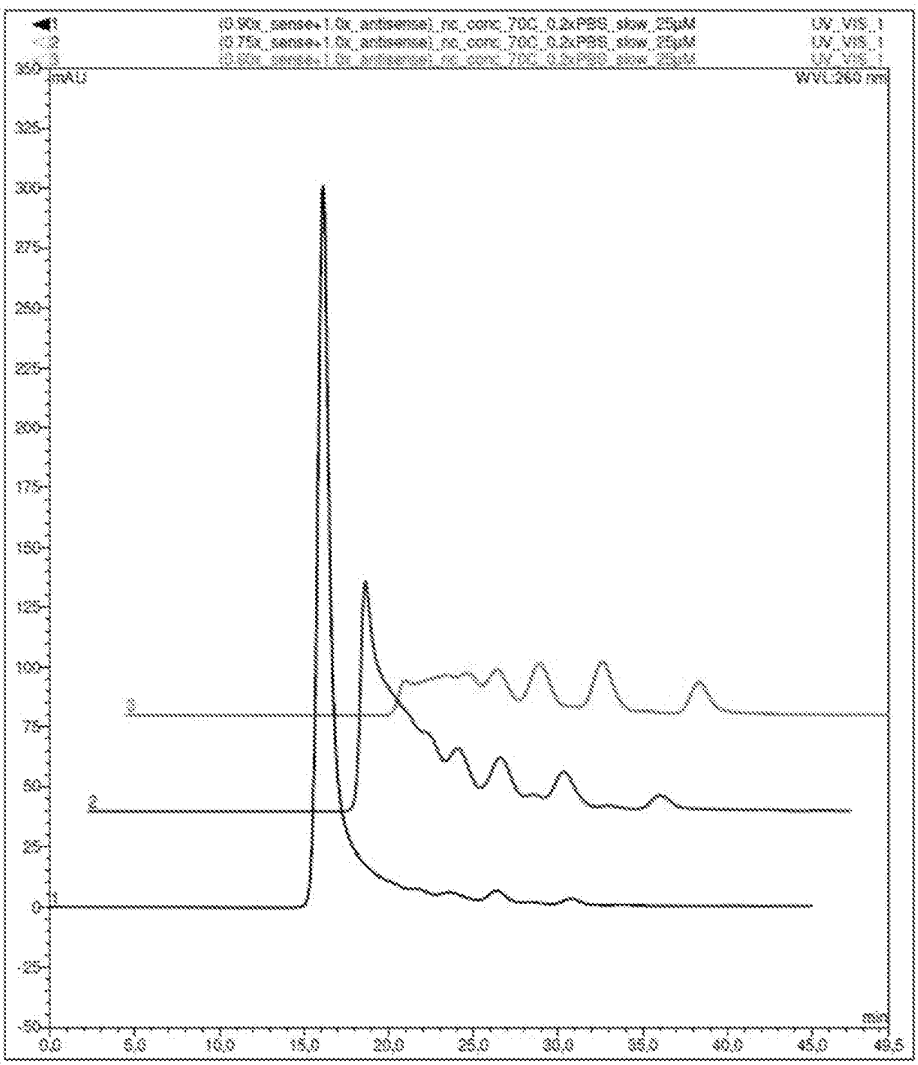


Fig. 34A presents the gel for sample nos. 1-15, which is discussed in connection with Example 22.

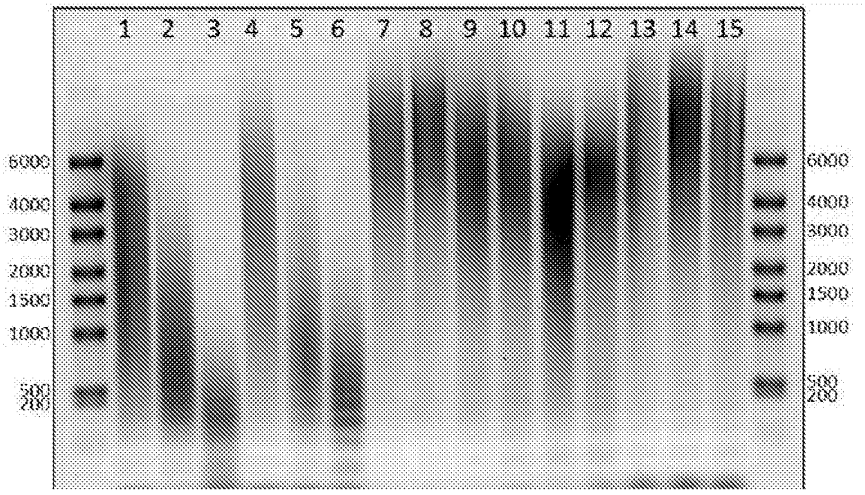


Fig. 34B presents the gel for sample nos. 1'-10', which is discussed in connection with Example 22.

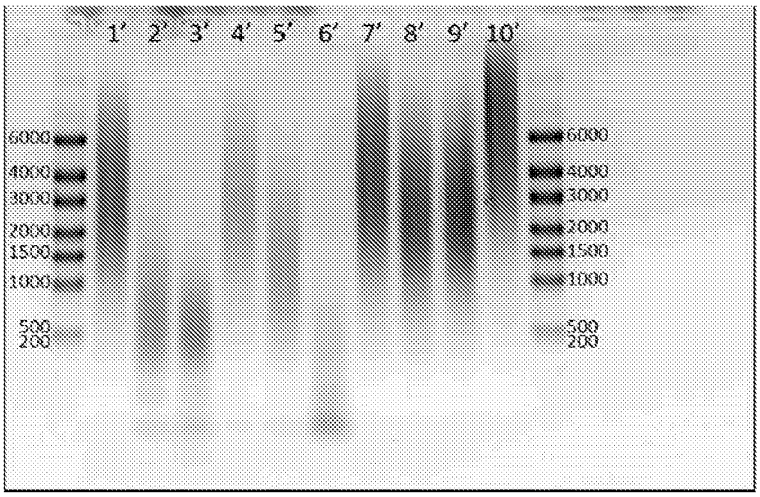


Fig. 35 presents data showing FVII activity determined from mouse serum in animal experiment MausRNAi-TV29, which is discussed in connection with Example 23.

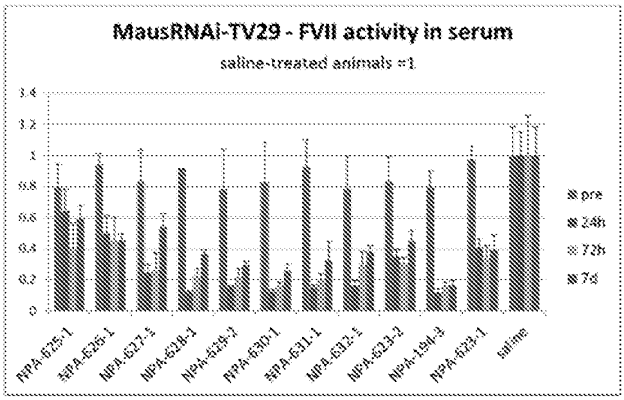


Fig. 36 presents data showing FVII activity determined from mouse serum in animal experiment MausRNAi-TV30, which is discussed in connection with Example 23.

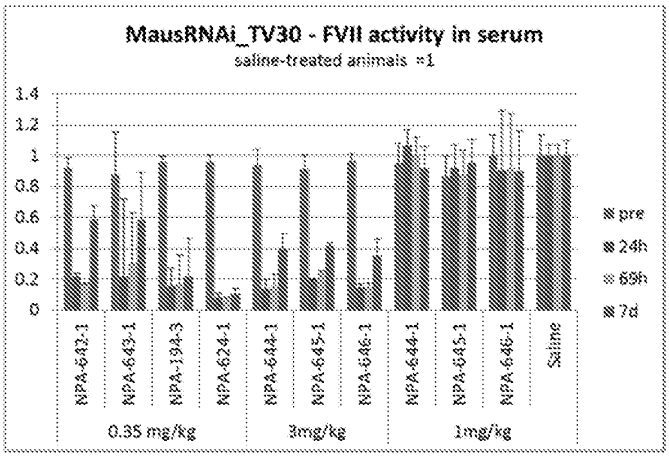


Fig. 37 presents a FVIIs-FVIIas heterodimer (X12714), which is discussed in connection with Example 24.

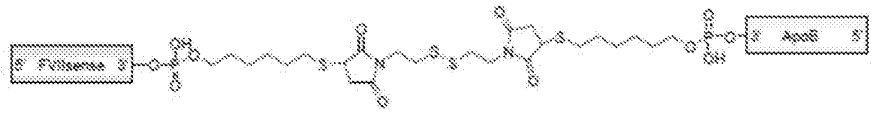


Fig. 38 presents a gel analysis of heterodimer X12714 (Lane 12), which is discussed in connection with Example 24.

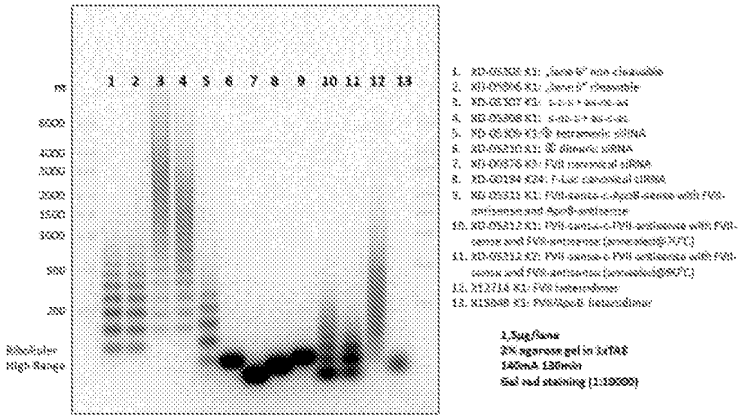
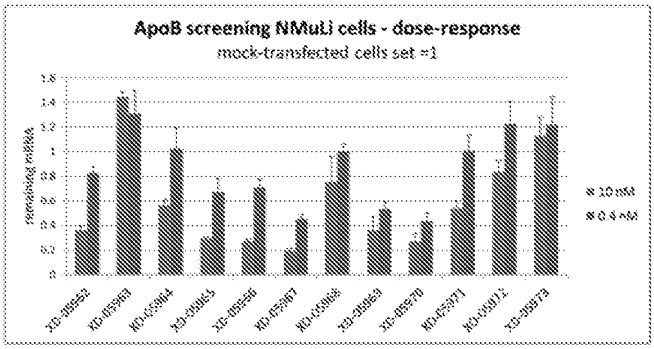


Fig. 39 presents dose-response data for ApoB screening NMuLi cells, which is discussed in connection with Example 26.



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