Figure 1a

Various Crosslinking Chemistries to Synthesize HA Hydrogel

1) Aldehyde (diol oxidation) – amine reductive amination

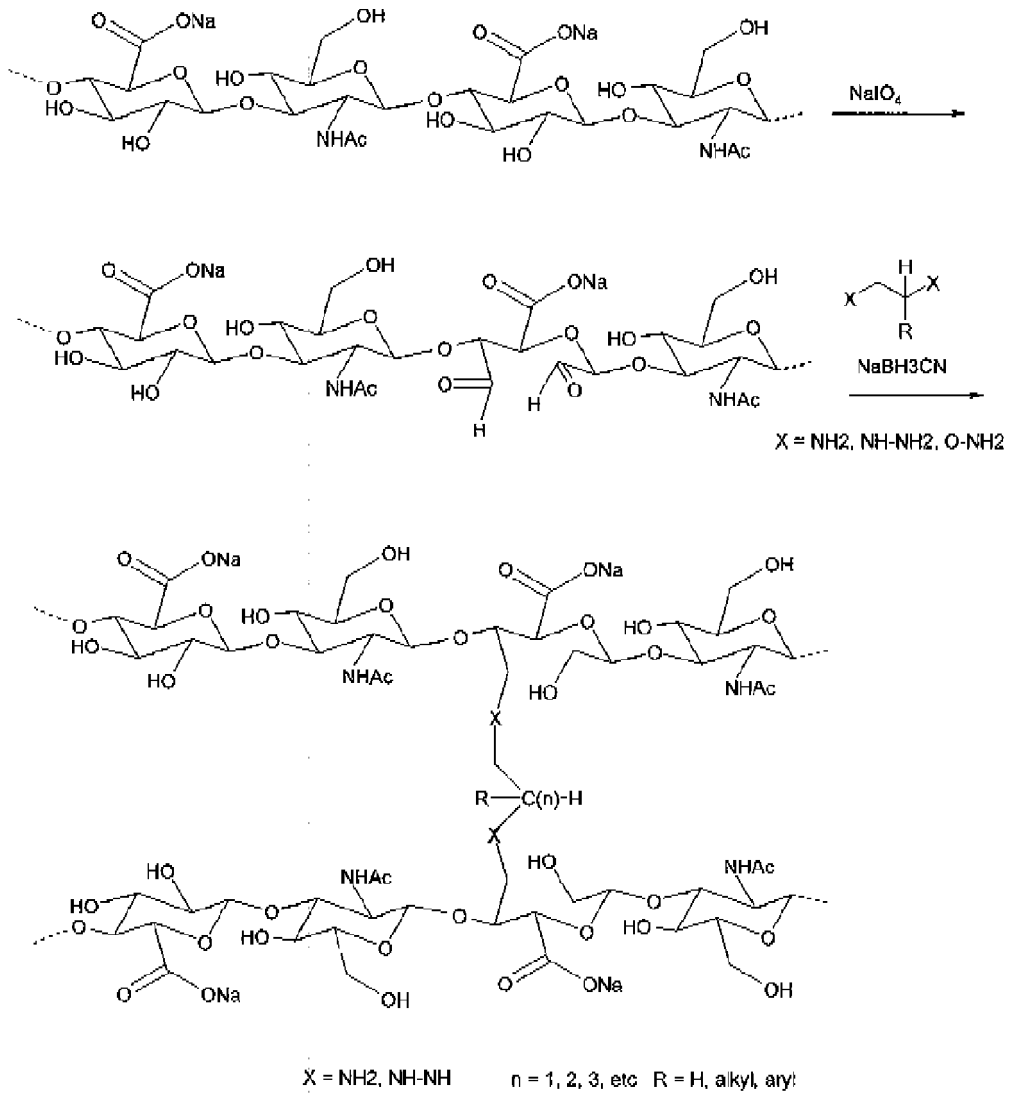
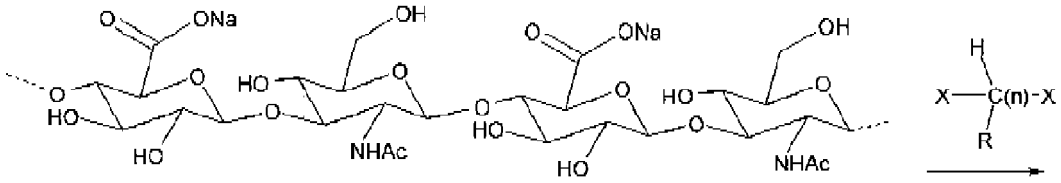
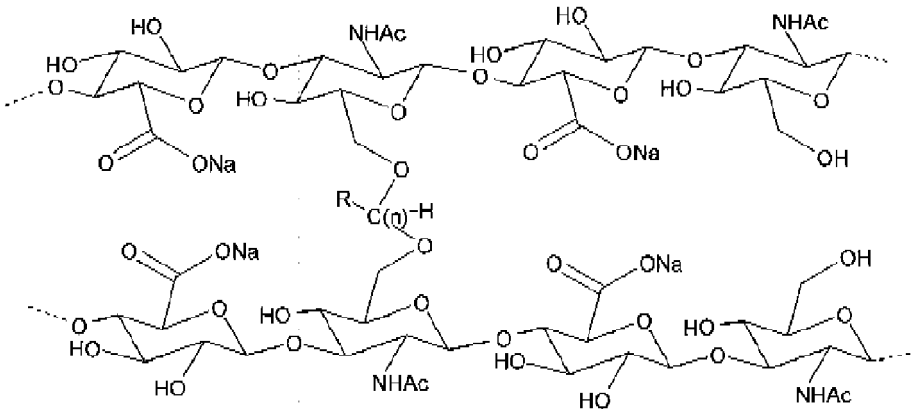


Figure 1a /2

2) Hydroxyl mediated alkylation



n = 2, 3,4, etc R = H, alkyl, aryl X = halo, sulphonate, other leaving group



3) Auto-crosslinking

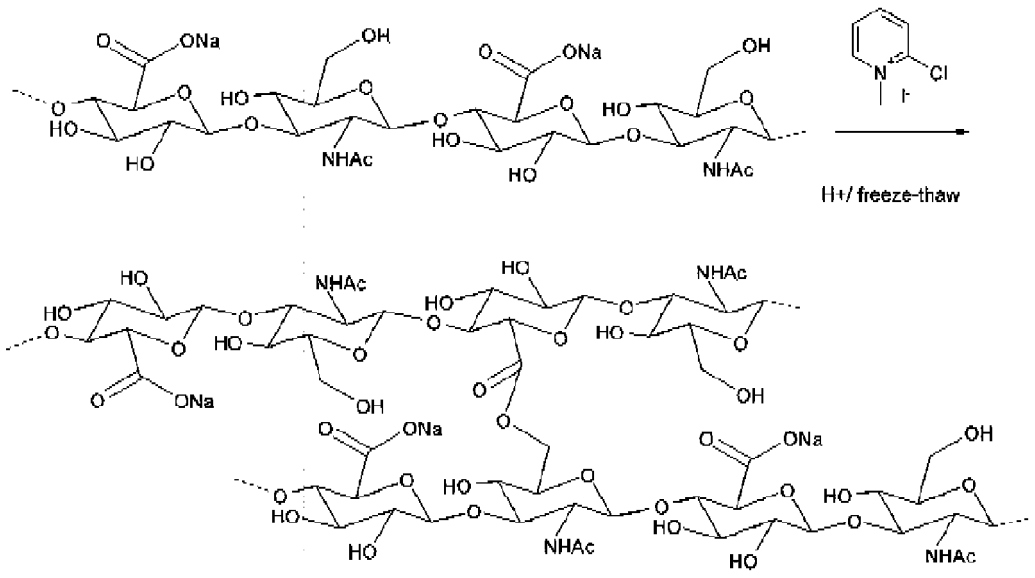


FIGURE 1b

Various Crosslinking Chemistries to Synthesize HA Hydrogel

4) Michael Addition Crosslinking (Thiol – maleimide)

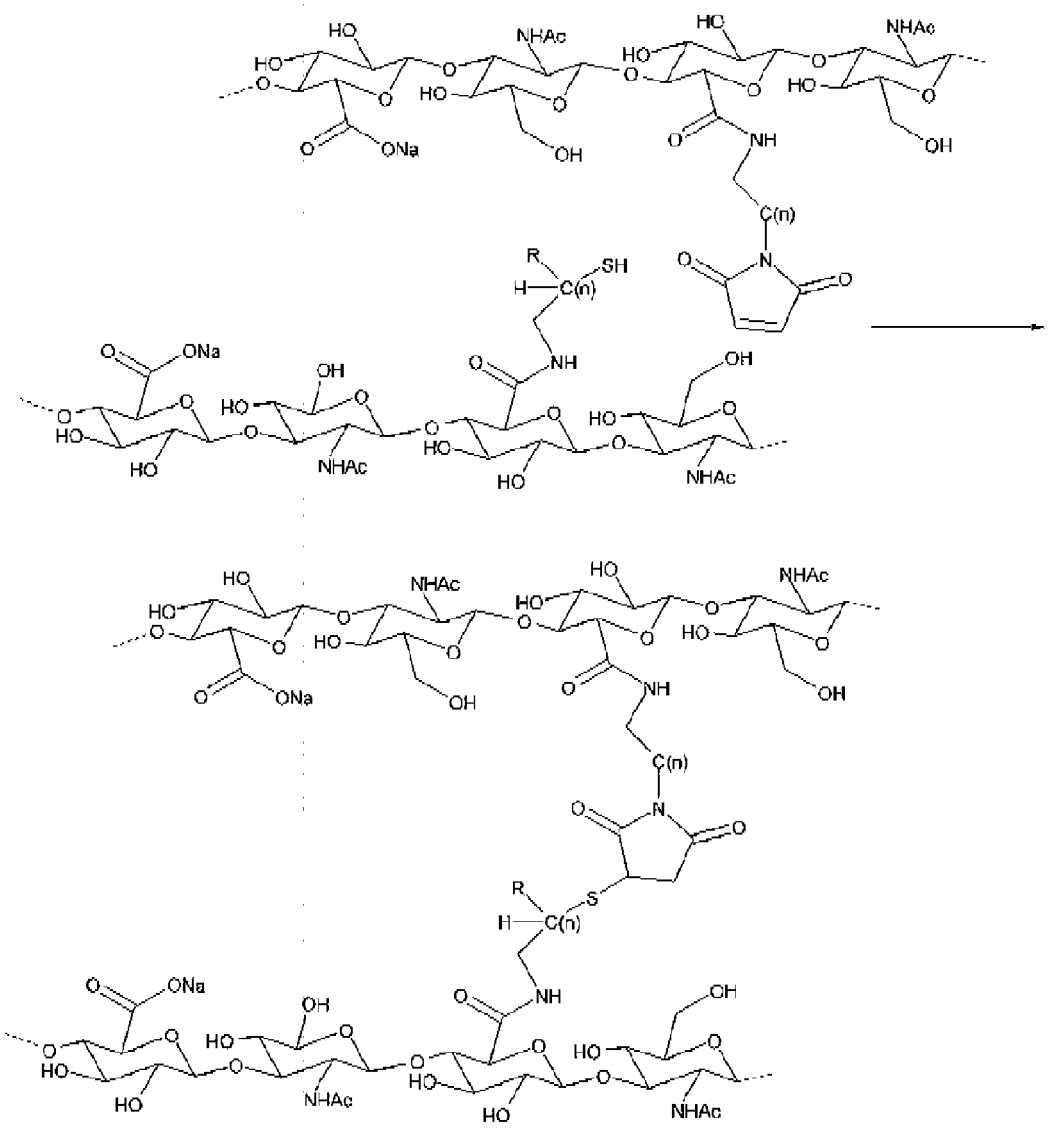
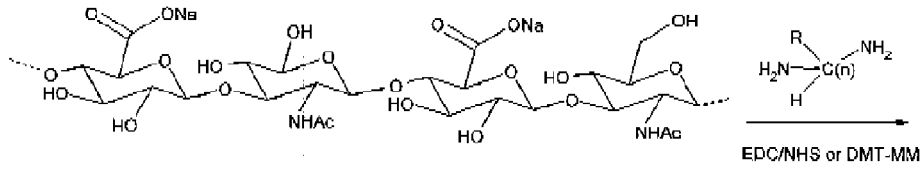
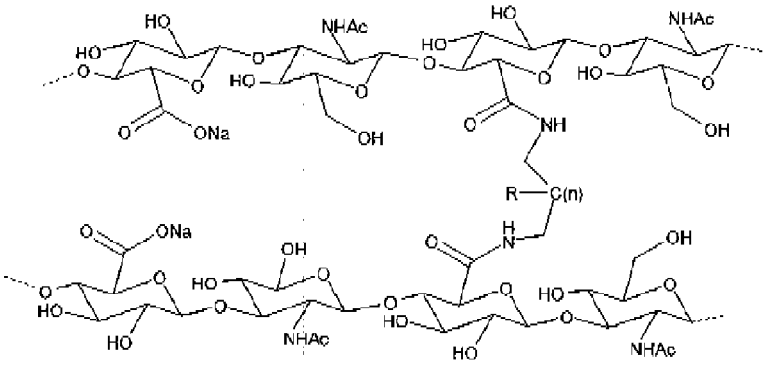


Figure 1b /2

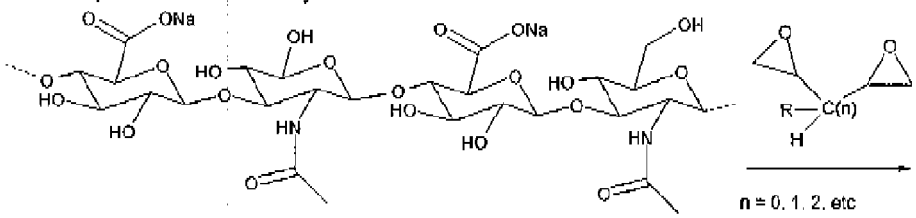
5) Amide Reaction



n = 2, 3, 4 etc R = H, alkyl, aromatic, heteroaromatic diaminoacid ester etc



6) Diol – Epoxide Chemistry



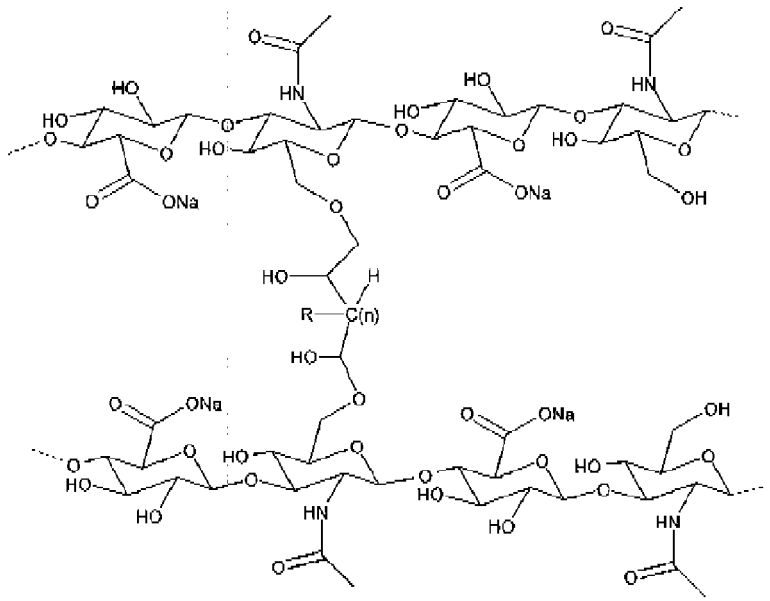


Figure 1c

Click Chemistries

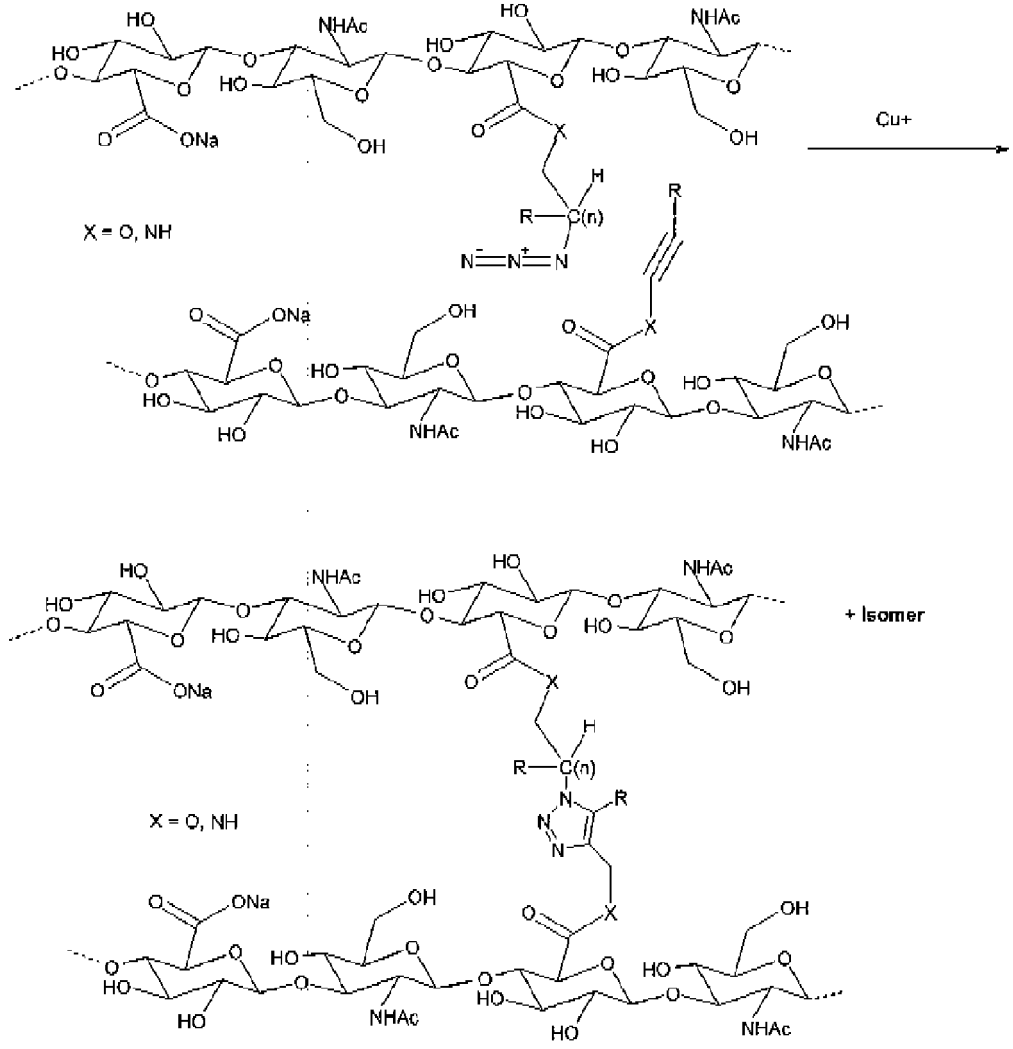


Figure 1c /2

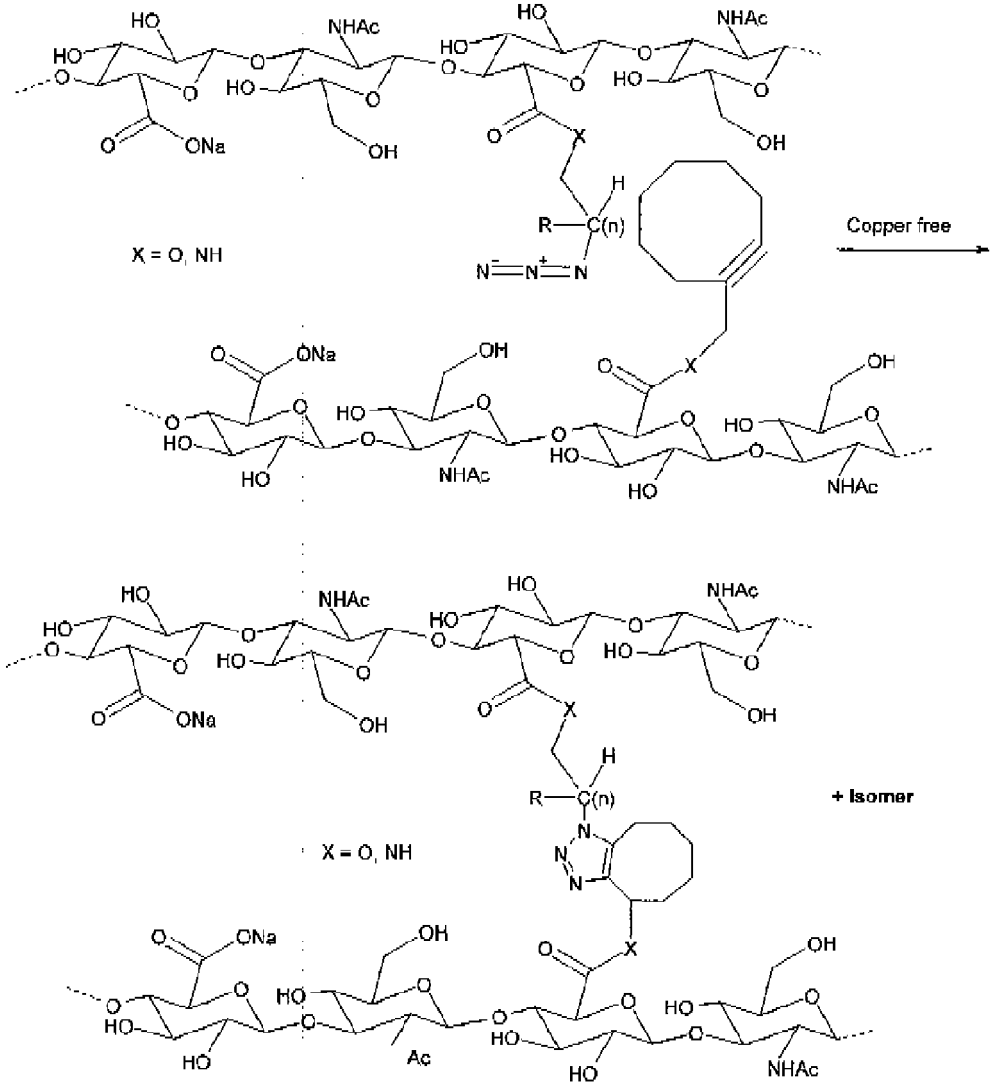


Figure 1c /3

2 +2 Cycloaddition

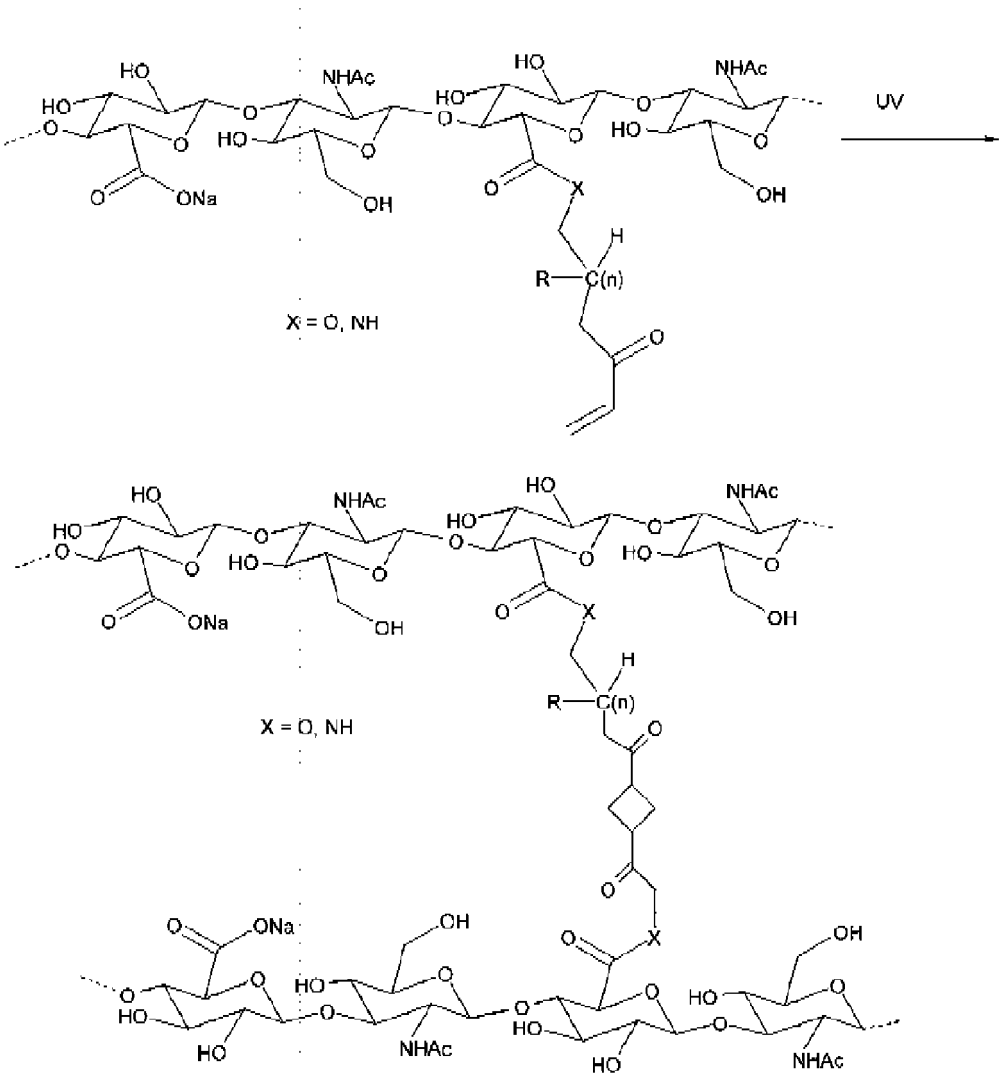


Figure 1c /4

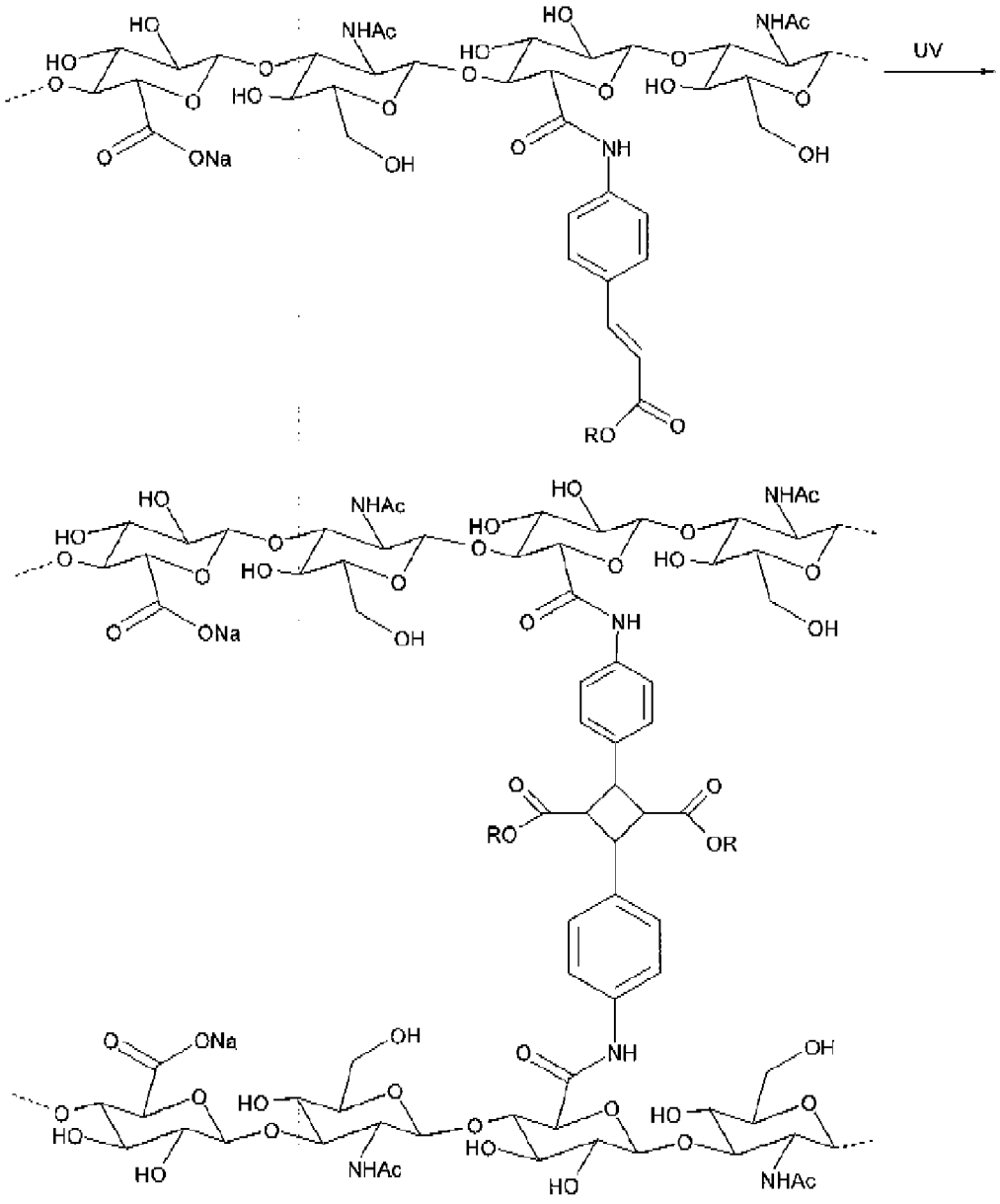
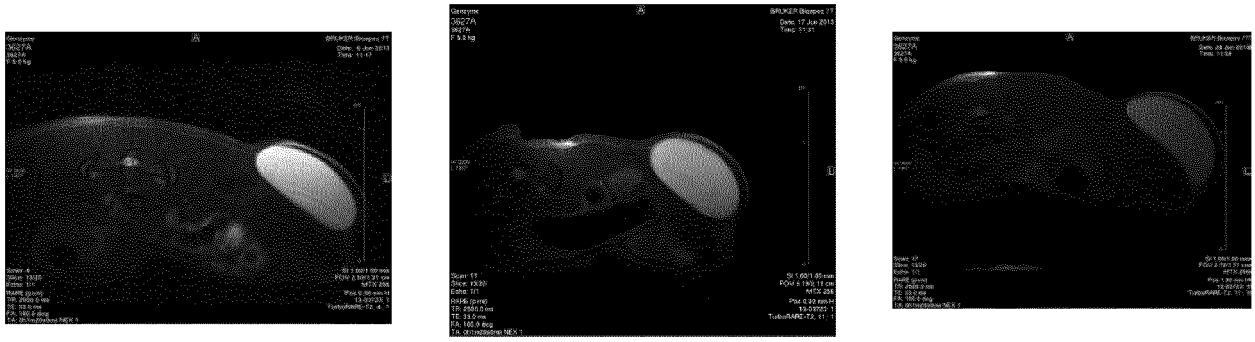
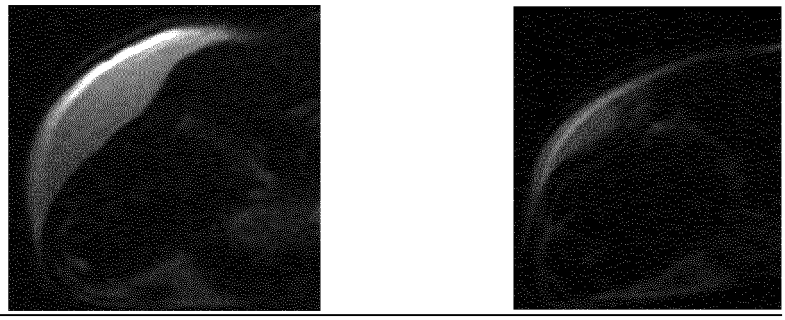


Figure 2a



Day 4 Day 15 Day 26

Figure 2b



Day 1 Day 4

Figure 3

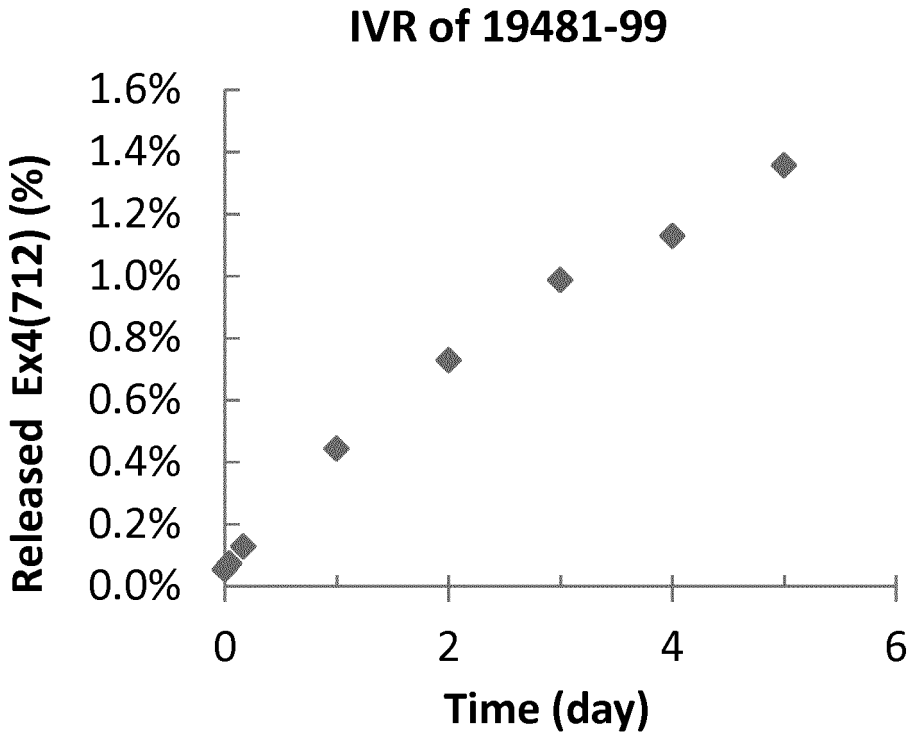

IVR of 19481-99
Released Ex4(712) (%)
1.6%
1.4%
1.2%
1.0%
0.8%
0.6%
0.4%
0.2%
0.0%
0
2
4
6
Time (day)

Figure 4

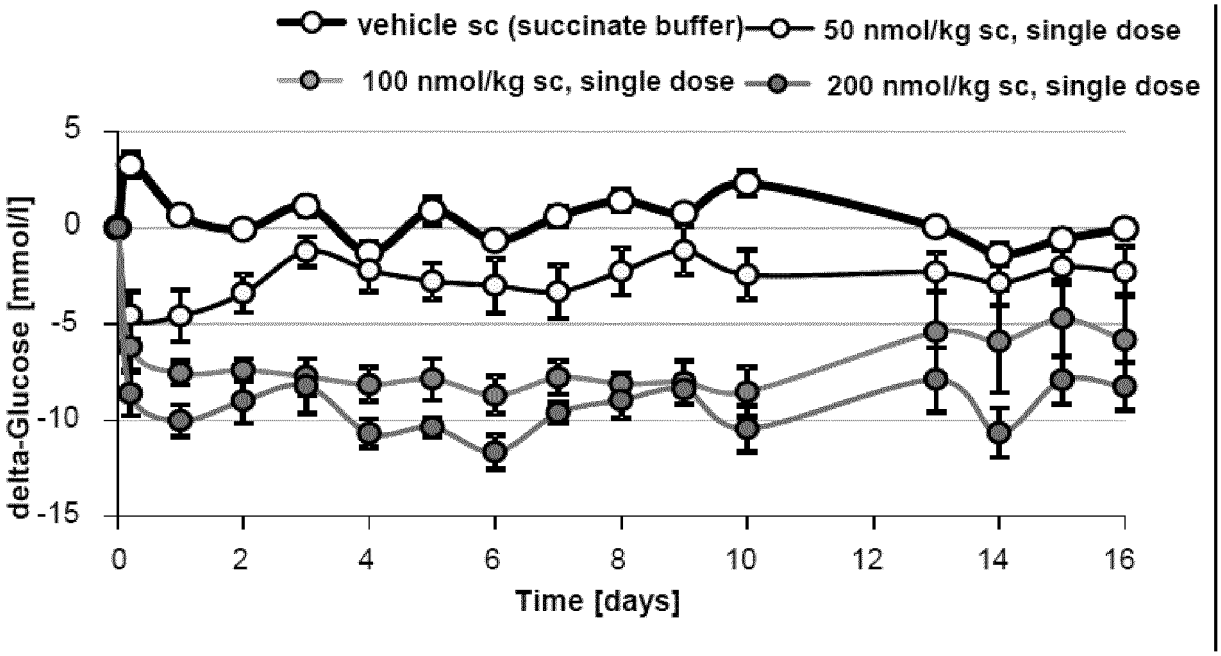

vehicle sc (succinate buffer)
50 nmol/kg sc, single dose
100 nmol/kg sc, single dose
200 nmol/kg sc, single dose
delta-Glucose [mmol/l]
5
0
-5
-10
-15
0
2
4
6
8
10
12
14
16
Time [days]

Figure 4b

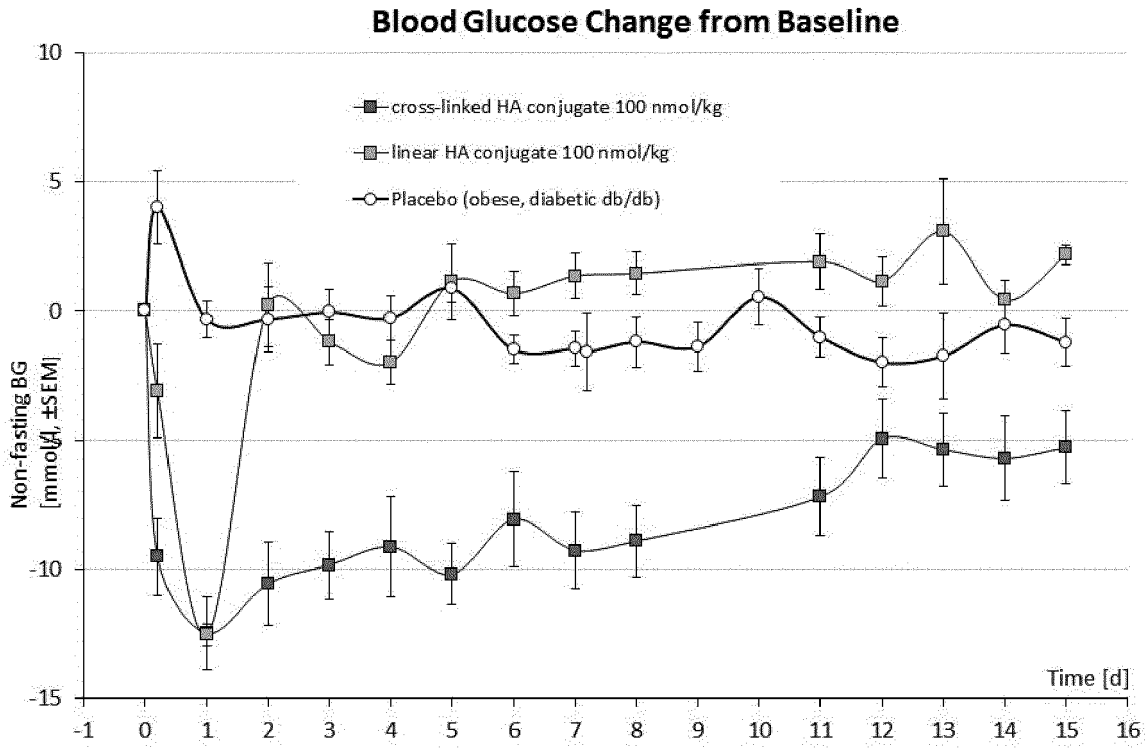
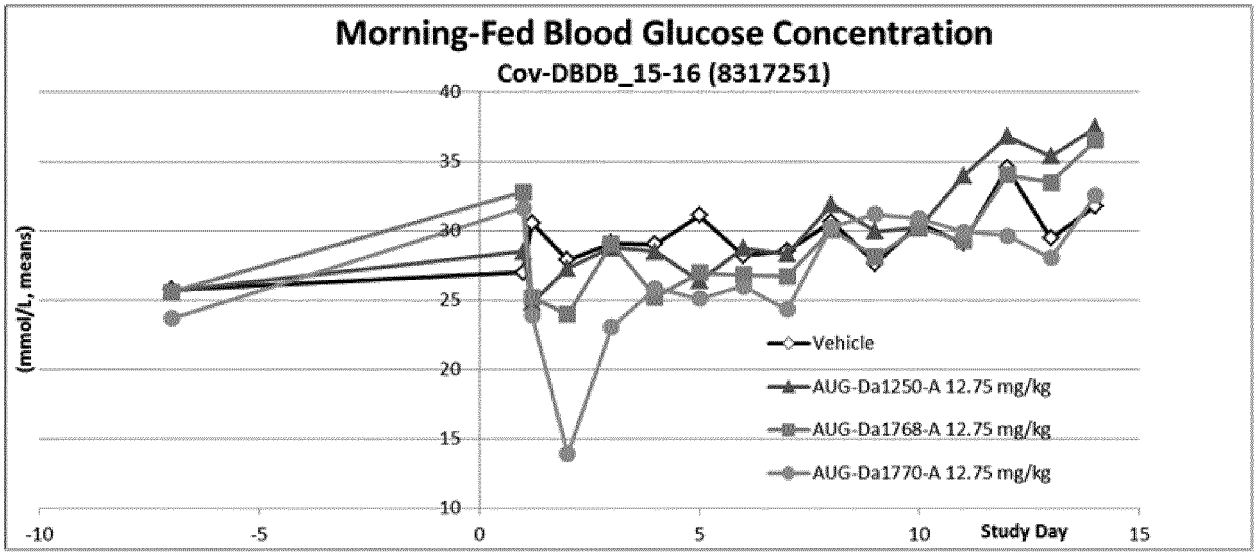

Blood Glucose Change from Baseline
cross-linked HA conjugate 100 nmol/kg
linear HA conjugate 100 nmol/kg
Placebo (obese, diabetic db/db)
Non-fasting BG [mmol/l, ±SEM]
Time [d]
10
5
0
-5
-10
-15
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16

Figure 4c


Morning-Fed Blood Glucose Concentration
Cov-DBDB_15-16 (8317251)
(mmol/L, means)
40
35
30
25
20
15
10
-10
-5
0
5
10
15
Study Day
Vehicle
AUG-Da1250-A 12.75 mg/kg
AUG-Da1768-A 12.75 mg/kg
AUG-Da1770-A 12.75 mg/kg

5

Figure 4d

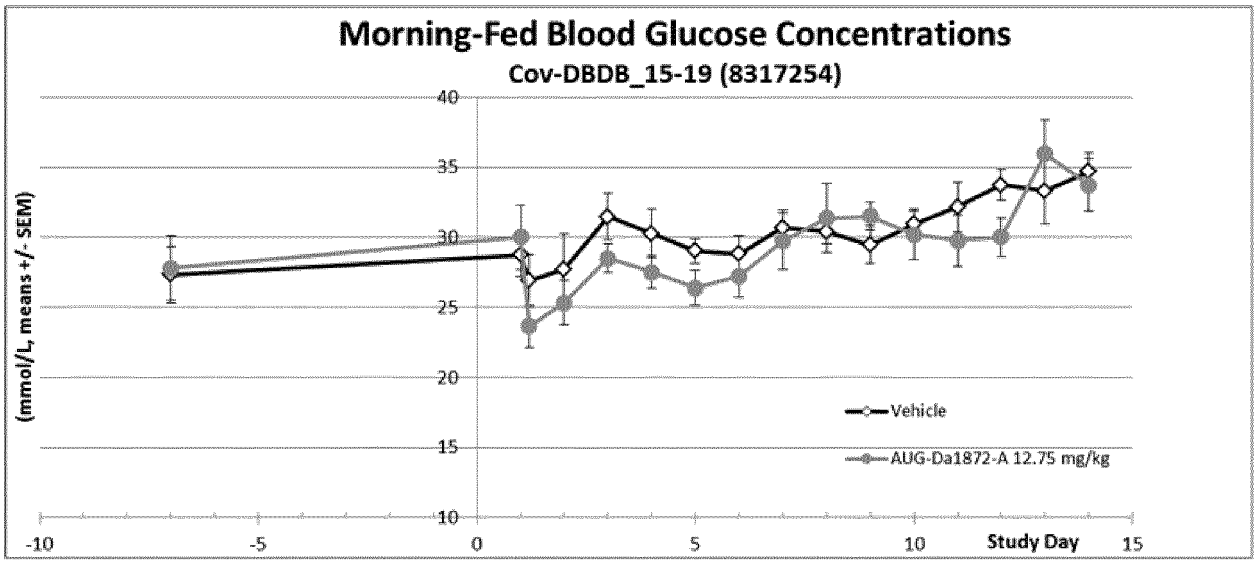

Morning-Fed Blood Glucose Concentrations
Cov-DBDB_15-19 (8317254)
(mmol/L, means +/- SEM)
40
35
30
25
20
15
10
-10
-5
0
5
10
15
Study Day
Vehicle
AUG-Da1872-A 12.75 mg/kg

Figure 5

- 30G, 1" needle using 1mL syringe
- 2% HA-conjugate was mixed with 2% soluble HA at a 4:1 ratio
  - Effective HA-conjugate concentration is 1.6%

